



Quantification and comparison of insulin sensitizing property of aqueous extract of *Cinnamomum zeylanicum* bark with rosiglitazone in steroid induced insulin resistance in wistar rats

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ABSTRACT

To quantify and compare the insulin sensitizing property of aqueous extract of *C. zeylanicum* bark and rosiglitazone in dexamethasone induced insulin resistance. 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]. In a 12 day study period, rosiglitazone and CZE groups received respective drug treatments and dexamethasone dosing (4mg/kg or 8mg/kg) started from day 7 onwards. On day 12, Fasting and post IPGTT blood samples were collected and processed for glucose and insulin estimations. In both series, CZE 250mg/kg treatment showed significant reduction in mean fasting glucose and insulin compared to rosiglitazone 8mg/kg, 16mg/kg groups and dexamethasone controls ($P < 0.05$). The CZE 250mg/kg treatment improved HOMA-IR, HOMA-IS, FGIR and 30min post-IPGTT DI significantly compared to dexamethasone controls and rosiglitazone groups ($P < 0.05$) while, the 120min post-IPGTT DI among sensitizer groups was insignificant ($P > 0.05$). Neither dexamethasone nor sensitizer treatment groups interfered with insulin secretion during IPGTT as the IGI sustained > 0.4 . The peripheral glucose uptake (Gutt index) was significantly improved with rosiglitazone and CZE 250mg/kg treatments over dexamethasone controls ($P < 0.05$) but, there was no significant difference between rosiglitazone and CZE 250mg/kg groups ($P > 0.05$). The whole body insulin sensitivity (Matsuda index) significantly improved with CZE 250mg/kg compared to rosiglitazone and dexamethasone control groups ($P < 0.05$). The efficacy of CZE 250mg/kg in steroid induced insulin resistance over rosiglitazone treatment as demonstrated by improved insulin sensitivity indices is substantiated.

Keywords: insulin sensitivity, insulin resistance, Gutt index, insulinogenic index, HOMA, Matsuda index, FGIR.

INTRODUCTION

Some of the diabetic subjects predominantly have a defect in insulin secretion, while others may experience normal or even excessive insulin secretion. The latter subgroup of diabetics has insulin resistance as the primary flaw in their glucose homeostasis. Glucocorticoids are essential for the regulation of metabolism, normal operation of nervous, cardiovascular, skeletal and immune systems. They are also implicated in the pathogenesis of obesity, insulin resistance and metabolic syndrome. [1] The diabetogenic effect of glucocorticoid hormones results from both hepatic and peripheral resistance to the action of insulin. In the setting of glucocorticoid excess, insulin fails to normally suppress hepatic glucose production and to normally stimulate peripheral glucose utilization. [2] The decrease in insulin-stimulated peripheral glucose utilization reflects reduced insulin-induced glucose uptake into skeletal muscle [1], the primary site of insulin-mediated glucose disposal. [3] In the management of insulin resistance associated diabetes mellitus, two insulin sensitizer groups are widely available are TZDs and Biguanides but, adverse effects are the determining factors in the long term care.

Cinnamomum zeylanicum(CZE) has been positively tested recently in type 2 diabetics for its anti-diabetic effect. CZE is well known to display an insulin-enhancing activity appears to increase glucose uptake. The Cao, et al., a study reported *in-vitro* novel findings that *Cinnamon* extract and polyphenols with procyanidin type-A polymers exhibit the potential to increase the amount of TTP, IR β , and GLUT4 (Glucose Transporter-4) in 3T3-L1 Adipocytes.[4] A study by Karalee J. et.al., demonstrate that the MHCP is an effective mimetic of insulin. MHCP may be useful in the treatment of insulin resistance studying the pathways leading to glucose utilization in cells.[5] But, the extent of preventing insulin resistance and extent of sensitivity increased to insulin to be admitted.

Some Indices of insulin sensitivity (IS) and resistance (IR) are, in practice which include simple ratios and products of insulin and glucose levels at single time points or integrated over time during an OGTT as proposed by Perley et al.[6] and Yalow et al.[7] More complex formulas for indices of insulin sensitivity or insulin resistance have been suggested by several investigators such as Matthews et al.(HOMA)[8],Cederholm *et al.* (SI) [9],Guttet *al.* (ISI,120)¹⁰, Matsuda *et al.* (ISI (composite)).[11] Surrogate markers like insulinogenic index (IGI)[12], Fasting Glucose to insulin ratio (FGIR).[13] The above methods have been correlated well with more rigorous but laborious measurements of insulin sensitivity as measured by either the steady state plasma glucose method[12] the frequently sampled i.v. glucose tolerance test and minimal model method[14,15]or the gold-standard hyperinsulinemic-euglycemic clamp method.[16,17]In this scenario, this present study is undertaken to quantify, substantiate and compare the degree of steroid induced insulin resistance and improvement in sensitivity with CZE and rosiglitazone treatments by calculation of simple indices.

EXPERIMENTAL SECTION

Experimental 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: AEC/29//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+Dexamethasone4mg/kg(Dexa control)	Vehicle+Dexamethasone8mg/kg(Dexacontrol)
ROSI 8mg/kg+Dexa4mg/kg	ROSI 8mg/kg+ Dexa8mg/kg
ROSI 16mg/kg+ Dexa4mg/kg	ROSI 16mg/kg+ Dexa8mg/kg
CZE 250mg/kg+ Dexa4mg/kg	CZE250mg/kg +Dexa8mg/kg

Plant material and extraction

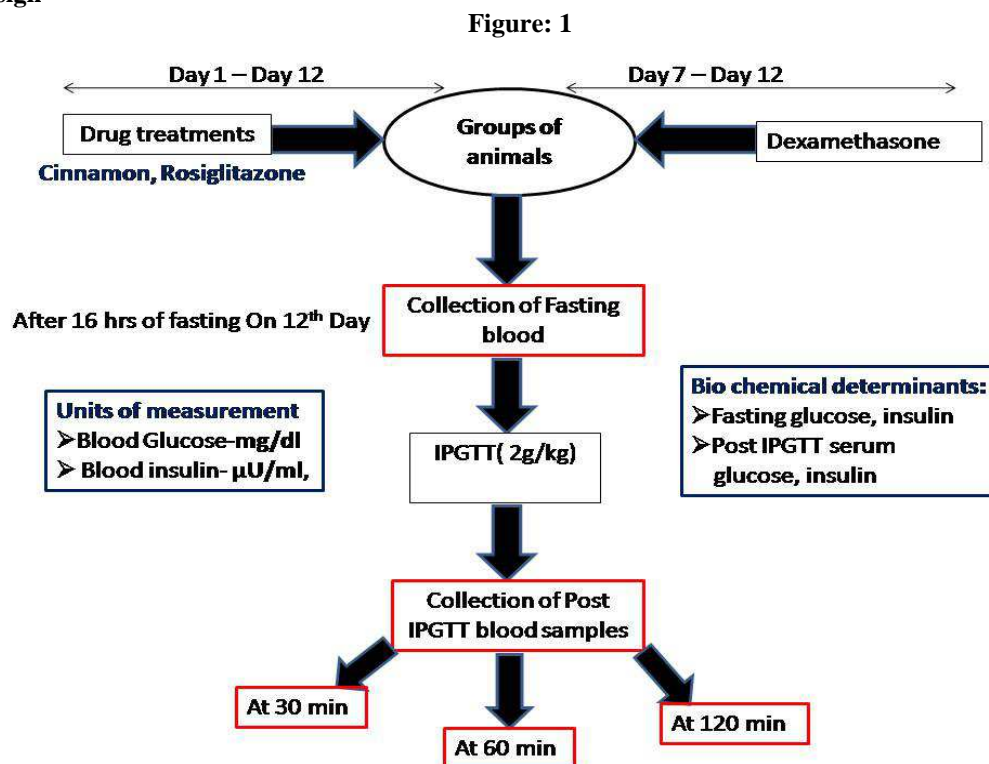
Cinnamomum zeylanicum(dalchiniin Kannada) is commonly known as cinnamon, the bark was collected from the pharmacy department at KVG Ayurvedic Medical College & Hospital, Sullia, Karnataka, in the month of December 2012. The plant was identified and authenticated by a Botanist from Nehru Memorial College, 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 extractor using distilled water at 80°C temperature. The yield of aqueous extract was concentrated in a rotary evaporator at reduced pressure and allowed the water to evaporate completely.[18] 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

The 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 (CZE) solution was prepared at a concentration of 250mg/ml with distilled water and 250mg/kg BW orally given to the respective groups. A pure fine powdered form of rosiglitazone (ROSI) 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.

Study design



Except dexamethasone, all the animals in all the groups (Table.1) 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, the 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). (Fig.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[19].

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. [20]

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 (µU/ml) by subjecting to linear regression equation in MS Excel 2010 version. The values were presented as Mean±SD.

Formulas used to calculate the indices:

$$\text{HOMA-IR} = \text{Fasting insulin} \times \text{Fasting glucose} \div 405$$

$$\text{HOMA-IS} = 10000 \div \text{fasting insulin} \times \text{fasting glucose}$$

$$\text{Insulinogenic index (IGI)} = (I_r - I_0) \div (G_r - G_0)$$

$$\text{Disposition Index (DI)} = (I_{30} - I_0) \div (G_{30} - G_0) \times \text{ISI}_{(\text{Matsuda})} [21]$$

$$\text{Fasting Glucose to insulin ratio (FGIR)} = G_0 / I_0$$

$$\text{Gutt index} = \text{ISI}_{0, 120} = \frac{500 + (G_0 - G_{120}) \times 0.19 \times \text{body wt}}{120 \times G_{\text{mean}} \times \log(I_{\text{mean}})}$$

$$\text{Matsuda index ISI}_{(\text{Matsuda})} = \frac{10000}{\sqrt{G_0 \times 10 \times G_{\text{mean}} \times I_{\text{mean}}}}$$

The HOMA-IR and HOMA-IS were used to determine the degree of hepatic insulin resistance and sensitivity respectively. The insulinogenic index was determined to assess the insulin secretion as well as β -cell function while, the disposition index and glucose to insulin ratio were determined to understand the improvement in glucose intolerance and glycemic variability with the treatment. The Gutt and Matsuda indices were determined to assess the improvement in peripheral and whole body insulin resistance respectively.

RESULTS

Fasting serum glucose and insulin

The comparative effects of the CZE and ROS Ion hyperinsulinemia and hyperglycemia induced by dexamethasone in both the series are displayed in Figure 2&3. CZE 250mg/kg significantly reduced fasting glucose and insulin levels compared to dexamethasone control and ROSI 8, 16mg/kg groups in both D4 and D8 series ($P < 0.05$). However, these were not significant between ROSI 8, 16mg/kg ($P > 0.05$) (Table 2&3).

HOMA-IR & IS

The degree and extent of insulin resistance and sensitivity was assessed in respective study groups by Homeostatic model assessment (HOMA) of IR and IS. As shown in the Table 2&3 the dexta control in both the series exhibited maximum rise IR and reduction in IS which is significant over plain control ($P < 0.05$). The mean values in ROSI and CZE groups significantly higher compared to dexta control, whereas, the difference in means of IR and IS between ROSI and CZE significantly varied, suggesting better improvement with CZE treatment in both the series ($P < 0.05$). However, the difference in means of IR and IS was not significant between ROSI 8mg/kg and 16mg/kg ($P > 0.05$). But, an observation made that neither ROSI nor CZE showed better mean values of IR and IS compared to plain control.

FGIR

The FGIR was significantly trimmed back in the dexta control group compared to plain control, CZE and ROSI 8mg/kg groups ($P < 0.05$) but not with ROSI 16mg/kg group ($P > 0.05$) in D4 series, whereas, in D8 series dexta control showed reduction in FGIR but it is non-significant compared to both ROSI treatment groups ($P > 0.05$). CZE 250mg/kg treatment significantly improved the ratio compared to all groups in both the series ($P < 0.05$) (Table no: 2& 3).

Sensitivity indices

In both the series The Gutt and Matsuda indices were determined in order to understand the improvement in peripheral and whole body insulin resistance respectively caused by dexamethasone (Table no: 2&3). In dexta control group Gutt index significantly lowered compared to ROSI and CZE groups in both the series ($P < 0.05$). The CZE and ROSI groups showed substantial improvement in Gutt index compared to dexta control in D4 series ($P < 0.05$) but, there is no significant difference observed among ROSI 8mg/kg, 16mg/kg and CZE groups ($P > 0.05$). In D8 series the CZE group improved Gutt index significantly compared to dexta control and ROSI 16mg/kg ($P < 0.05$) but not with 8mg/kg ($P > 0.05$) and there is no significant difference observed between ROSI 8mg/kg and 16mg/kg groups ($P > 0.05$) as well.

The Matsuda index was significantly dampened in dexta control groups in both the series compared to ROSI and CZE treatments ($P < 0.05$). The CZE 250mg/kg treatment significantly increased the Matsuda index compared to rest of the study groups ($P < 0.05$) but, did not meet the plain control mean value in both the series whereas this index did not significantly differ between ROSI treatments ($P > 0.05$) in both the series (Table no: 2&3).

Disposition index (DI)

The post-IPGTT DI was determined by applying appropriate mathematical formula and the values are mentioned in Figure 4. In both the series, at 30min post-IPGTT, CZE and ROSI treatments significantly improved the DI compared to dexta control in both the series ($P < 0.05$). The DI hasn't significantly varied between ROSI and CZE groups ($P > 0.05$). Nevertheless, there is no significant difference observed in DI between ROSI 8mg/kg and 16mg/kg ($P > 0.05$) while, the mean values of DI at 120min post-IPGTT did not indicate significant difference among ROSI 8mg/kg, 16mg/kg and CZE 250mg/kg groups in both the series ($P > 0.05$).

Insulinogenic index (IGI)

The IGI in all the study groups was maintained above baseline (< 0.4) as the insulin secretion was noted normal or above normal levels in all the study groups throughout the post-IPGTT. The maximum IGI was noted at 120min post-IPGTT in a dexta control group of both the series, which is substantial compared to ROSI 8mg/kg, 16mg/kg, CZE 250mg/kg treatment and plain control groups ($P < 0.05$) (Table no: 4).

Figure: 2 Fasting glucose and insulin values on day 12 in D4 series

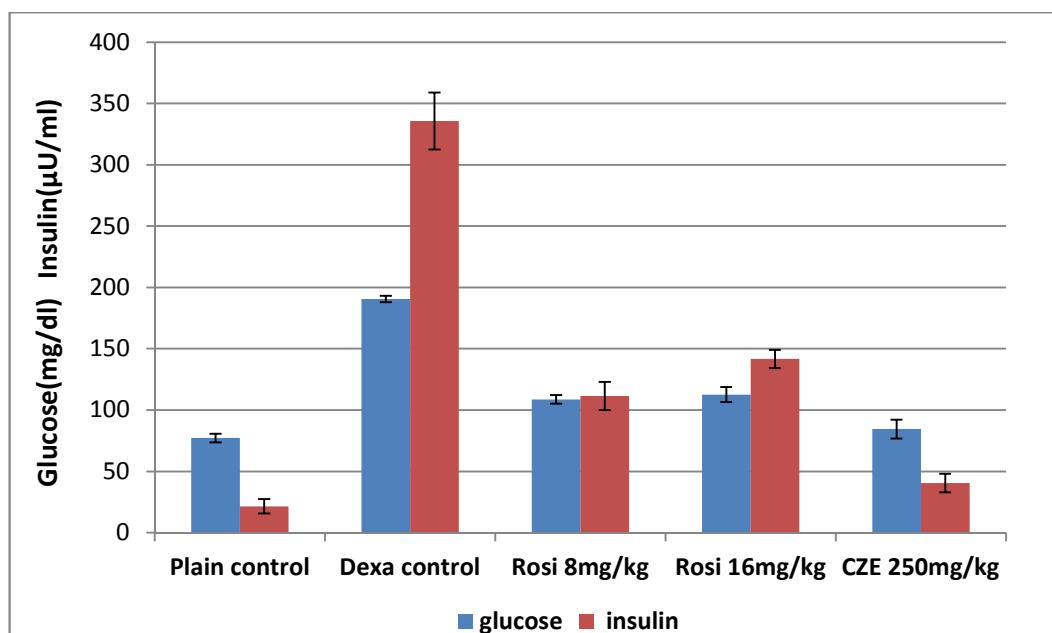


Figure: 3 Fasting glucose and insulin values on day 12 in D8 series

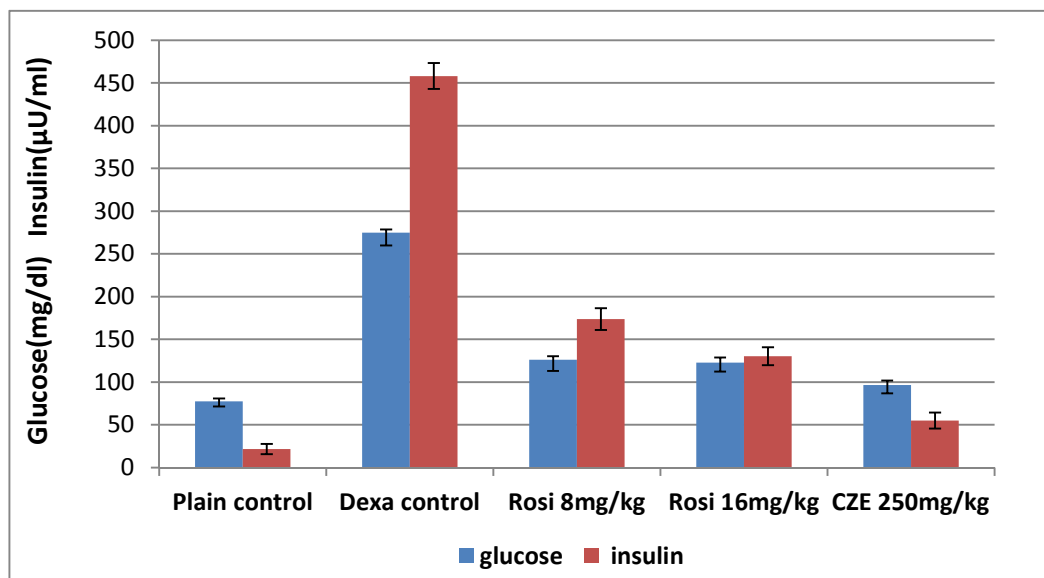


Table no: 2 Differences in means of surrogate indices of insulin resistance and sensitivity on day 12 in D4 series

Surrogate markers	PC	Dexa control (4mg/kg)	ROSI 8mg/kg	ROSI 16mg/kg	CZE 250mg/kg
Fasting glucose	77.2±3.6	190.5±2.6	108.7±3.5 ^a abe	112.6±6.2 ^a abe	84.6±7.7 ^a bcd
Fasting insulin	21.5±5.9	335.7±23.3	111.5±11.4 ^a abe	141.7±7.4 ^a abe	40.5±7.5 ^a abcd
FGIR	3.59±1.36	0.55±0.41	0.98±0.12 ^a abe	0.79±0.06 ^a ae	2.42±0.40 ^a abcd
HOMA-IR	4.0±0.7	147.9±18.4	29.8±2.3 ^a abde	39.3±2.6 ^a abce	9.6±2.3 ^a abcd
HOMA-IS	6.3±1.7	0.10±0.03	0.82±0.06 ^a abe	0.61±0.05 ^a abe	2.67±0.6 ^a abcd
Gutt index	0.52±0.031	0.0087±0.004	0.021±0.016 ^a ab	0.033±0.030 ^a ab	0.035±0.011 ^a ab
Matsuda index	2.76±0.83	0.12±0.04	0.60±0.07 ^a abe	0.52±0.06 ^a abe	1.83±0.58 ^a abcd

Note: *= significant at 5% level ($P < 0.05$), a= plain control (PC); b= Dexa control; c= ROSI 8mg/kg; d= ROSI 16mg/kg; e= CZE 250mg/kg.

Table no: 3 Differences in means of surrogate indices of insulin resistance and sensitivity on day 12 in D8 series

Surrogate markers	PC	Dexa control (8mg/kg)	ROSI 8mg/kg	ROSI 16mg/kg	CZE 250mg/kg
Fasting glucose	77.2±3.6	274.7±3.9	125.9±4.4 ^a abe	122.8±5.8 ^a abe	96.3±5.5 ^a abcd
Fasting insulin	21.5±5.9	458.0±15.1	173.6±12.8 ^a abde	130.2±10.5 ^a abce	54.9±9.5 ^a abcd
FGIR	3.59±1.36	0.64±0.22	0.72±0.03 ^a ade	0.94±0.08 ^a ae	1.58±0.37 ^a abcd
HOMA-IR	4.0±0.7	310.6±29.8	54.0±5.8 ^a abde	39.3±3.1 ^a abce	11.3±1.7 ^a abcd
HOMA-IS	6.3±1.7	0.07±0.03	0.45±0.04 ^a abe	0.62±0.04 ^a abe	2.20±0.35 ^a abcd
Gutt index	0.52±0.20	0.0013±0.00	0.017±0.00 ^a ab	0.011±0.00 ^a ab	0.029±0.00 ^a ab
Matsuda index	2.76±0.83	0.06±0.02	0.37±0.09 ^a abe	0.51±0.13 ^a abe	1.15±0.77 ^a abcd

Note: *= significant at 5% level ($P < 0.05$), a= plain control (PC); b= Dexa control; c= ROSI 8mg/kg; d= ROSI 16mg/kg; e= CZE 250mg/kg.

Figure: 4 Post IPGTT Disposition index values on day 12 in D4 and D8 mg/kg series

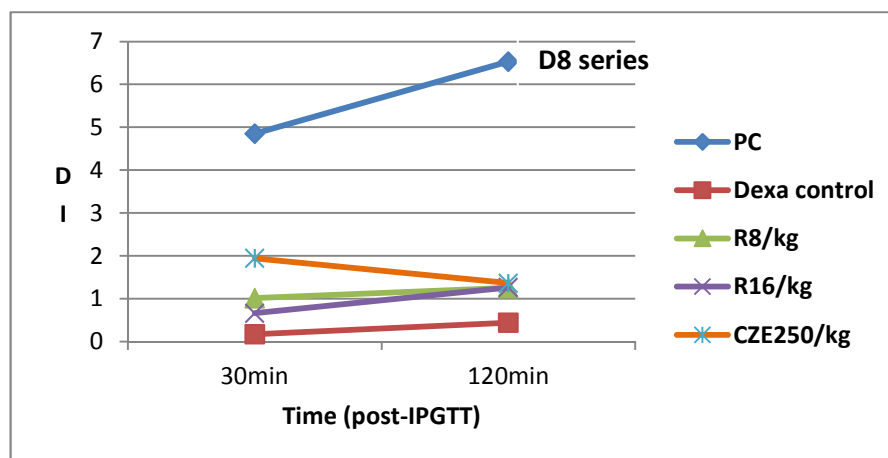
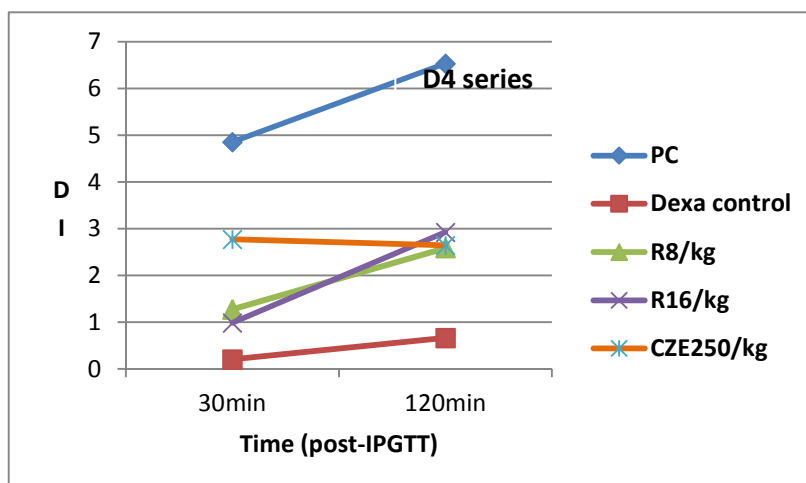


Table no: 4 Differences in means of post-IPGTT insulinogenic index on day 12 in D4 & D8 series

Group	30min		60min		120min	
	D4	D8	D4	D8	D4	D8
PC	1.81±0.7	1.81±0.7	1.93±0.8	1.93±0.8	2.60±1.1	2.60±1.1
Dexa control	1.57±0.5	1.93±0.3	0.88±0.2	0.62±0.08	5.23±1.5	7.77±1.9
ROSI 8/kg	2.12±0.1 ^{abe}	2.65±0.4 ^{abde}	2.62±0.8 ^{abc}	3.14±1.9 ^{abde}	4.60±2.0 ^{ac}	3.11±1.0 ^{ab}
ROSI 16/kg	1.84±0.4 ^{bc}	1.35±0.1 ^{bc}	1.98±0.8 ^{bc}	0.96±0.2 ^{ac}	5.43±3.1 ^{ac}	2.56±0.9 ^{abc}
CZE250/kg	1.19±0.1 ^{acd}	0.82±0.1 ^{abc}	1.62±0.4 ^c	0.55±0.07 ^{ac}	0.88±0.7 ^{bcd}	1.19±0.5 ^{abd}

Note: * = significant at 5% level ($P < 0.05$), a = plain control (PC); b = Dexa control; c = ROSI 8mg/kg; d = ROSI 16mg/kg; e = CZE 250mg/kg.

DISCUSSION

Till date, studies on anti-diabetic activity of *Cinnamomum zeylanicum* in various models revealed its insulin secretion enhancing property [22] but, none of the studies explained its insulin sensitizing property *in vivo* and its use in insulin resistance. This work is aimed at the extent of insulin sensitizing activity by depriving steroid induced IR of *C. zeylanicum* bark extract (CZE) in comparison with rosiglitazone (ROSI). The study period and standardized doses of 4mg, 8mg/kg dexamethasone were chosen from the pilot study for the induction of insulin resistance. The two dose ranges of dexamethasone chosen to observe the dose dependent elevation and severity of IR

The standardized dexamethasone doses produced peak insulinaemia and glycaemia as it is known to produce. Various surrogate markers were determined in this study to quantify and compare the dexamethasone induced insulin resistance and sensitivity with CZE and ROSI treatments and assessed the improvement as well.

The results found in this study revealed that, the insulin sensitizing potential of CZE in steroid induced insulin resistance is greater than or equal to that of ROSI as CZE reduced the insulin and glycaemic levels during fasting state compared to dexa control and ROSI treatments. The ground for beneficial property is CZE have insulin like and unique effects on the regulation of gene expression.[23]

The Homeostatic model assessment (HOMA) was employed to determine the hepatic IR and IS of in respective study groups in both the series. Dexamethasone controlled animals showed maximum hepatic IR and lowest hepatic IS values among all study groups in respective series as the IR and IS are inversely proportional to each other.[24] this explains the potential of glucocorticoids in the induction of insulin resistance as they inhibit the activation of glucose transport in rat skeletal muscle by both insulin and non-insulin related stimuli.[25] The rise in hepatic IR with dexamethasone was effectively prevented with CZE and ROSI treatments evidenced by improved hepatic IR and IS values, but the CZE treatment overtook the ROSI treatment in preventing hepatic IR and improving IS in both the series.

The IGI was employed to determine the alteration in insulin secretion in response to dexamethasone and along with ROSI and CZE treatments in D4 and D8 series. As Sood A, Ismail-Beigi F concluded their study[26], the dexamethasone did not affect the synthesis and production of insulin from the islets of β -cells rather it potentiated the secretion as the IGI was noted maximum at 120min post-IPGTT in the dexa control group compared to rest of the groups. This means, the dexamethasone induced the latter phase of insulin secretion than the first phase in response to glucose load. This increase in insulin secretion was even higher than plain control. This reflection is on par with studies done by John Set al and Takeshi O et al,[27, 28] suggest that the IGT can cause by dexamethasone. The ROSI and CZE treatments as well did not affect the secretion of insulin compared to the tentative cut-off value of IGI (0.4) throughout the Post-IPGTT and effectively prevented the dexamethasone induced IGT in animals.

The FGIR also reduced markedly in the dexa control group in both the series and the ROSI and CZE treatments improved the ratio significantly. This states that the IS was severely dampened with dexamethasone treatment and ROSI and CZE prevented the loss of IS. However, FGIR spared well by CZE treatment rather than ROSI treatment. The glycaemic variability to IPGTT was determined by DI which explains the acute insulin response to amount of glucose.[29] According to the findings made from this study, the lowest DI observed with dexamethasone treatment as it produced maximum IR among all study groups in both the series. Hence, it is clear that acute treatment of high dose dexamethasone constrained glycemic variability and intolerance in animals. Nonetheless, the CZE and ROSI treatment deprived the fall in DI effectively and, the rise in glycemic variability was well controlled by both CZE and ROSI.

The whole body insulin sensitivity comprising of both hepatic and peripheral glucose uptake and several indices are available to assess them individually.[30] In present study Gutt index was employed to assess the extent of peripheral glucose uptake by the tissues, particularly skeletal muscles and adipose tissue, whereas, HOMA-IS was considered for extent of hepatic extraction of glucose in both the series. The dexamethasone treatment severely

hindered the peripheral glucose uptake while CZE and ROSI treatments enhanced a number compared to dexta control, but lower than plain control in both the series. However, the difference in improvement observed between ROSI and CZE was insignificant. With this we interpreted that the above insulin sensitizers enhance glucose uptake by hepatic extraction rather than uptake into skeletal muscles and adipose tissue.

The whole body IR was assessed from Matsuda index and it was markedly lowered the index suggesting an increase in whole body insulin resistance in animals and it was elevated with CZE and ROSI treatments in respective groups in both the series. This creates the sense that the whole body insulin sensitivity was preserved by CZE and ROSI treatments over dexamethasone treatment. The difference in Matsuda index was significant between CZE and ROSI treatments. Nevertheless, The overall difference among surrogate markers of IR and IS was insignificant between ROSI 8mg/kg and 16mg/kg treatments.

CONCLUSION

To conclude, the bark of *C.zeylanicum* has the insulin sensitising potential that can be compared with that of rosiglitazone and probably enhances insulin sensitivity primarily by hepatic extraction of glucose and by peripheral glucose uptake into skeletal muscles and adipose tissue. These aspects of insulin sensitivity required to be evaluated further to establish more precise insulin sensitizers.

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