Research Article

METHANOL AND WATER EXTRACTS OF *COSTUS SPECIOSUS* (J.KÖNIG) SM. LEAVES REVERSE THE HIGH-FAT-DIET INDUCED PERIPHERAL INSULIN RESISTANCE IN EXPERIMENTAL WISTAR RATSSubasinghe Hewa Walpola Amila Sewwandi¹, Hettihewa Lakshmi Menik², Gunawardena Sampath³, Liyanage Thusharie⁴¹BPharm Degree Programme, Faculty of Medicine, University of Ruhuna, Sri Lanka²Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Sri Lanka³Department of Physiology, Faculty of Medicine, University of Ruhuna, Sri Lanka⁴Department of Pathology, Faculty of Medicine, University of Ruhuna, Sri Lanka

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DOI: 10.7897/2230-8407.050209**ABSTRACT**

Worldwide prevalence of insulin resistance is growing rapidly and there is no specific treatment for this condition. Medicinal plants are being used as sources of novel drug discovery. The objective of this study was to investigate the effect of methanol and water extracts of *Costus speciosus* leaf on insulin resistant experimental Wistar rats. Male Wistar rats were divided into five groups (n = 6) and IR was induced by a high fat diet (19.13 % fats). CS leaf methanol extract and water extract were prepared. Rats were treated daily for four weeks with the extracts. Group 1: 0.5 % CMC 1 ml, Group 2: 500 mg/kg/day methanol extract in CMC, Group 3: 500 mg/kg/day water extract in CMC, Group 4: 1500 mg/kg/day water extract in CMC, Group 5: Pioglitazone 10 mg/kg/day. Serum was analysed for glucose, triglycerides and insulin at baseline and after the therapy. Insulin resistance was calculated using indirect indices; HOMA, QUICKI and McAuley. Data were analysed by one- way ANOVA followed by Bonferroni post-hoc test and student's t-test. Test values of $p < 0.05$ were considered statistically significant. Both CSLwex (at doses 500 and 1500 mg/kg) and CSLmex (500 mg/kg) significantly reduced ($p < 0.05$) insulin resistance and serum insulin level within four weeks therapy. Further, 500 mg/kg CSLmex reduced serum triglyceride level by 8.98 % in IR rats. Both *Costus speciosus* leaf water and methanol extracts have potent effect on reducing IR in experimental rats. Therefore, *Costus speciosus* leaf might be useful as a good source of insulin sensitizing chemical compounds.

Keywords: Insulin resistance, *Costus speciosus*, water extract, methanol extract, Wistar rats**INTRODUCTION**

The global prevalence of insulin resistance (IR) is escalating rapidly and many influencing environmental factors have been incriminated. Consumption of high fat diet has been proven as one of the main factors¹. IR is the pre-diabetic stage and type 2 diabetes (DM) is the end stage of it. In IR, insulin becomes less effective in lowering blood sugar, although it is available in sufficient amounts. It is due to the defects in insulin signalling pathways. IR is a major attributing factor of many diseases like hypertension, coronary heart diseases, dyslipidemia etc.² Therefore, a remedy which is therapeutically effective in IR will be a reliever of many metabolic diseases. Plants are being used in treatment of diseases since the dawn of human civilization. Nowadays, the knowledge on medicinal properties of plants has increased significantly and there is a growing trend of using medicinal plant parts as vegetable and herbal drinks. *Costus speciosus* (J.König) Sm. which belongs to family Costaceae is a medicinal plant which is commonly found in wet shady lands of the Asian region. In Sri Lankan Ayurvedic system, it is commonly used for the treatment of gastritis, leprosy, skin diseases, inflammatory diseases, anaemia and also in DM.³ Further, antihyperglycemic activity of *Costus speciosus* rhizome has been already scientifically proven.⁴ Some researchers had confirmed that crude extracts of *Costus speciosus* rhizome was beneficial in controlling diabetes in Wistar rats and among them the hexane extract was the most potent compound.⁵ In addition, both aqueous and methanolic extracts of *Costus speciosus* rhizome were highly effective in normalizing the blood glucose levels.⁶ Moreover, *Costus speciosus* is identified as a medicinal plant which consists of many therapeutically active agents⁷ and the two chemical

compounds, costunolide⁸ and eremanthin⁹ had demonstrated hypoglycemic and hypolipidemic activities in diabetic Wistar rats. Leaves of this plant are popular among Sri Lankans as 'sambol' in their main meals which is considered to control blood glucose and abnormal lipid profiles. Although many scientific investigations have done to prove the therapeutic actions of *Costus speciosus* rhizome, there are no research evidence for the effectiveness of its leaf. We could not trace a single research work related to reversing the insulin resistance either by rhizome or leaf. However, correcting pre-diabetic IR is important to prevent DM and its complications. Therefore, this study was designed to probe the insulin sensitizing effect of *Costus speciosus* leaf on naturally induced IR rat model as an initial step of drug designing.

MATERIALS AND METHODS**Collection of plant materials**

Costus speciosus (J.König) Sm. leaves were collected from a wet shady land in Matara district, Sri Lanka. The plant was authenticated by Mrs. R.A.S.W. Ranasinghe, National Herbarium, Peradeniya, Sri Lanka. A voucher specimen was deposited (No SS/2012/01) at the National Herbarium for future references.

Preparation of plant extract

Water extract (CSlwex) was prepared by refluxing the dried powder of *Costus speciosus* fresh leaf (400 g) in distilled water (3 L) using Soxhlet apparatus at 50°C for 6 hours. The extract was filtered through a Buchner funnel and the water was removed under the reduced pressure in a rotary evaporator at 60°C. The concentrated crude extract was freeze dried until a constant weight was obtained. Methanol extract

(CSImex) was prepared by refluxing the dried material of *Costus speciosus* leaf (400 g) in absolute methanol (3 L) using Soxhlet apparatus at 40°C for 6 hours. After the refluxing, the extract was filtered through a Buchner funnel. Then the filtrate was evaporated under reduced pressure using rotary evaporator at 40°C to remove excess methanol. The crude extract was subjected for freeze drying until a constant weight was obtained.

Animals

Eight weeks old Male Wistar rats which were inbred at Medical Research Institute, Colombo were used. All the rats were within the weight range of 170-250 g. They were housed in the cages at temperature $25 \pm 2^\circ\text{C}$ at the animal house, Faculty of Medicine, University of Ruhuna. They were allowed for free access to water and pellet diet. Prior to the initiation of the experiment, the rats were acclimatized to animal house conditions for two weeks. Ethical approval was obtained from the Ethical Review Committee of Faculty of Medicine, University of Ruhuna, Sri Lanka.

Induction of insulin resistance

Insulin resistance was induced by feeding a high fat diet (HFD) for three months. This diet was prepared in-house and it contained 19.13 % of total fat. Induction of IR was confirmed by three standard indirect indices; Homeostasis Model Assessment (HOMA)¹⁰, Quantitative Insulin Sensitivity Check Index (QUICKI)^{11,12} and McAuley index (McA)¹³. HOMA was calculated by $\text{Insulin } (\mu\text{IU/mL}) \times \text{Glucose (mmol/L)} / 22.5$; QUICKI by $1 / (\log \text{insulin } (\mu\text{IU/mL}) + \log \text{glucose (mg/dL)})$ and McA by $\exp [2.63 - 0.28 \ln (\text{insulin } (\mu\text{IU/mL}) - 0.31 \ln (\text{Triglyceride (mmol/L)})]$. HOMA ≥ 2.6 , QUICKI ≤ 0.33 and McA ≤ 5.8 were considered as insulin resistant.¹¹

Experimental procedure

Thirty IR rats were randomly divided into five groups (n = 6) and treated with *Costus speciosus* extracts as below. Group 1: 0.5 % carboxy methyl cellulose (CMC), group 2: 500 mg/kg CSImex, group 3: 500 mg/kg CSIwex, group 4: 1500 mg/kg CSIwex, group 5: 10 mg/kg pioglitazone (Figure 1). Methanol extract and pioglitazone were given in 1 mL of 0.5 % (w/v) CMC while water extract was given in 1 mL of freshly prepared distilled water. Treatment was done daily for 4 weeks using an oral feeding tube. Rats were fasted for 12 hours and blood was drawn from the lateral tail vein at the baseline and after four weeks *Costus speciosus* treatment. Serum was separated by centrifuging blood at 3500 rpm for ten minutes. It was stored at -20°C until analyzed.

Analytical methods

Serum glucose (GOD-PAP method) and triglyceride (GPO method) were measured using test kits (BIOLABO, France). Assay of glucose and triglyceride (TG) were performed and absorbance was measured at 490 nm. Serum insulin was analyzed using Enzyme Linked Immunosorbent Assay method (diagnostic automation/Cortes diagnostics, Inc. USA). Insulin assay via absorbance was measured at 450 nm wave length using an automated microplate reader (Bio-tek instruments, Inc.)

Statistical analysis

Data were analysed by one- way ANOVA followed by Bonferroni post-hoc test and student's t-test. Test values of $p < 0.05$ were considered statistically significant. Data were presented as mean $\pm$ SE.

Table 1: Baseline values of biochemical parameters and IR indices in different rat groups

Group	Glucose (mmol/L)	Triglyceride (mmol/L)	Insulin ($\mu\text{IU/mL}$)	HOMA	QUICKI	McA
0.5 % CMC	6.75 ± 0.22	1.97 ± 0.08	10.78 ± 3.52	3.41 ± 1.0	0.321 ± 0.013	5.83 ± 0.49
500 mg/kg CSImex	6.75 ± 0.30	2.07 ± 0.10	10.76 ± 1.13	3.26 ± 0.36	0.322 ± 0.006	5.73 ± 0.12
500 mg/kg CSIwex	6.81 ± 0.30	2.04 ± 0.08	10.68 ± 0.46	3.34 ± 0.26	0.320 ± 0.004	5.78 ± 0.14
1500 mg/kg CSIwex	6.70 ± 0.28	2.07 ± 0.14	12.83 ± 0.52	3.84 ± 0.22	0.314 ± 0.002	5.41 ± 0.17
10 mg/kg pioglitazone	6.92 ± 0.50	1.94 ± 0.07	10.64 ± 0.91	3.24 ± 0.28	0.322 ± 0.004	5.86 ± 0.09

Table 1- indicates the baseline values of Glucose (mmol/L), Triglycerides (mmol/L), insulin ($\mu\text{IU/mL}$) and insulin resistance indices of different groups. Values are given as Mean $\pm$ SE. There were no significant differences among the groups in any of the parameters mentioned above ($p > 0.05$).

Table 2: Effect of *Costus speciosus* extracts on different biochemical parameters of insulin resistant Wistar rats after one month therapy

Drug	Glucose (mmol/L)		Triglyceride (mmol/L)		Insulin ($\mu\text{IU/mL}$)	
	Baseline	After therapy	Baseline	After therapy	Baseline	After therapy
0.5 % CMC	6.75 ± 0.22	8.04 ± 0.76	1.97 ± 0.08	2.31 ± 0.25	10.78 ± 3.52	6.86 ± 1.74
500 mg/kg CSImex	6.75 ± 0.30	8.19 ± 0.77	2.07 ± 0.10	1.89 ± 0.11	10.76 ± 1.13	3.14 ± 0.23^a
500 mg/kg CSIwex	6.81 ± 0.30	10.15 ± 0.96	2.04 ± 0.08	2.32 ± 0.14	10.68 ± 0.46	3.41 ± 0.45^a
1500 mg/kg CSIwex	6.70 ± 0.28	8.71 ± 0.53	2.07 ± 0.14	2.35 ± 0.04	12.83 ± 0.52	3.87 ± 0.36^a
10 mg/kg pioglitazone	6.92 ± 0.50	6.78 ± 0.52	1.94 ± 0.07	2.55 ± 0.21	10.64 ± 0.91	7.76 ± 0.70

Table 2- indicates baseline and final serum glucose (mmol/L), triglyceride (mmol/L) and insulin ($\mu\text{IU/mL}$) of insulin resistant Wistar rats. Values are given as Mean $\pm$ SE. ^adenotes statistical significance in comparison with 10 mg/kg pioglitazone group at $p < 0.05$ after one month therapy.

Figure 1: Illustration of the treatment plan of *Costus speciosus* therapy

The treatment plan of *Costus speciosus* leaf extracts, pioglitazone and CMC on insulin resistant Wistar rats, during one month study period. CMC- carboxy methyl cellulose, CSLmex- methanol extract of *Costus speciosus* leaf, CSLwex- water extract of *Costus speciosus* leaf.

Figure 2 indicates HOMA values in different groups of rats treated with methanol and water extract of *Costus speciosus*, CMC and pioglitazone (mean ± SE). a denotes statistical significance ($p < 0.05$) compared to final HOMA of 0.5 % CMC treated group.

Figure 3: Baseline and final QUICKI values in different rat groups

Figure 3 indicates QUICKI values in different groups of rats treated with methanol and water extract of *Costus speciosus*, CMC and pioglitazone (mean $\pm$ SE). a denotes statistical significance compared to final McA of 0.5 % CMC treated control group ($p < 0.05$).

Figure 4: Baseline and final McA values in different rat groups

Figure 4 indicate baseline and final McA values in different groups of rats treated with methanol and water extract of *Costus speciosus*, CMC and pioglitazone (mean $\pm$ SE). a and b respectively denote statistical significance compared to final McA of CMC and pioglitazone ($p < 0.05$) groups.

RESULTS

Table 1 shows the baseline values of fasting blood glucose, TG and insulin of our study groups. In addition to that, the baseline IR values were also shown by all three indirect indices. $\text{HOMA} \geq 2.6$, $\text{QUICKI} \leq 0.33$ and $\text{McA} \leq 5.8$ were considered as the deciding levels for insulin resistance. We could not find significant differences among the groups in Glucose, TG, Insulin, HOMA, QUICKI and McA before the commencement of the study (Table 1).

Effects of *Costus speciosus* on HOMA

We found that significant changes in peripheral insulin resistance by all three *Costus speciosus* extracts after four weeks. HOMA values among five groups were significantly different ($p < 0.05$) after one month therapy. 500 mg/kg CSLmex had decreased HOMA by 60.1 % ($p < 0.05$). 500 mg/kg and 1500 mg/kg CSLwex also had reduced HOMA by 51.47 % ($p < 0.05$) and 60.33 % ($p < 0.05$) respectively. Pioglitazone had reduced it only by 25.62 % ($p > 0.05$). Figure 2 shows that, HOMA of all three extracts at baseline

were not significantly different, but they were significant ($p < 0.05$) compared to control values (0.5 % CMC) after one month therapy.

Effects of *Costus speciosus* on QUICKI

We further found that, CSLwex at 500 and 1500 mg/kg doses and 500 CSLmex had reduced IR by QUICKI (11.96 %, 15.4 % and 14.55 %) at the end of the treatment. In addition, QUICKI of 500 CSLmex and 1500 CSLwex became significantly different from control CMC group ($p < 0.05$, Figure 3) after the therapy.

Effects of *Costus speciosus* on McA

With the McA analysis, 500 CSLmex and 1500 mg/kg CSLwex significantly reduced IR by McA by 47.99 % ($p = 0.003$) and 44.93 % ($p = 0.013$) respectively compared to baseline but, 500 mg/kg CSLwex had not shown any significant change in IR by McA (34.23 %, $P > 0.05$). At the end of the treatment, there was a significant difference in McA of all three extracts compared to CMC and pioglitazone by Bonferroni post-hoc test ($p < 0.05$, Figure 4).

Effect of *Costus speciosus* extracts on serum insulin, triglyceride and glucose

There was no significant difference in serum insulin concentrations between the groups at the baseline. But, it became significant after one month *Costus speciosus* therapy ($F = 6.88$, $p = 0.002$). Serum insulin was found to decrease significantly ($p < 0.05$) by all three extracts (500 mg/kg CSLmex by 70.84 %, 500 mg/kg CSLwex by 68.07 % and 1500 mg/kg CSLwex by 69.86 %). Further, this effect is significant ($p < 0.05$) compared to pioglitazone treated rats (Table 2). Pioglitazone showed only 27.05 % reduction in insulin concentration compared to baseline. Table 2 shows that, an increase of fasting glucose levels from baseline in rats treated with 500 mg/kg CSLmex, 500 mg/kg CSLwex and 1500 mg/kg CSLwex and it was 21.32 %, 48.89 % and 29.98 % respectively while 10 mg/kg pioglitazone reduced it by 1.94 %. There was no significant change in TG after the four weeks *Costus speciosus* therapy but, 500 mg/kg CSLmex reduced it by 8.98 %. Further, there are slight increases of TG levels in water extracts treated groups but, the changes are not significant ($p > 0.05$) compared to baseline TG levels (Table 2).

DISCUSSION

Remarkably growing prevalence of insulin resistance has become a worldwide problem because it is associated with the pathogenesis of many metabolic diseases such as type 2 diabetes mellitus, dyslipidemia, cardio vascular diseases and polycystic ovarian syndrome. There are no specifically approved medications to treat insulin resistance so that diabetes medications, for instance, metformin and thiazolidinediones are used as insulin sensitizers. Thus, there is a strong necessity of finding a specific drug which may possibly reverse the mechanism of developing IR. As the present global trend is towards the drug sources from medicinal plants, we focused on the leaves of *Costus speciosus* plant in which, the rhizome is proved for hypoglycemic, hypolipidemic and anti-inflammatory actions. Hence insulin resistance induced rats by feeding a high fat diet, were treated with CSLmex and CSLwex for four weeks and its insulin sensitizing, hypoinsulinemic, hypoglycemic and hypotriglyceridemic actions were assessed. In this study, we attempted to induce of IR naturally (without using

chemicals) in rats, by feeding a fatty diet formulation. According to the previous reports, HFD can cause IR through an induction of local inflammatory action in peripheral insulin sensitive tissues, mainly in adipocytes.¹⁴ There, pro-inflammatory cytokines like IL-6 and TNF- α , by induction of inflammation can impair the receptor binding capacity of insulin, contributing to the development of IR and type 2 diabetes in later.¹⁵⁻¹⁷ Although there are many research work conducted in related to the *Costus speciosus* rhizome's hypoglycaemic effects, there is lack of evidence related to the leaves. Our study shows for the first time that, both methanol and water extracts of *Costus speciosus* leaf decreased peripheral insulin resistance, leading to the correction of adipose tissue insulin resistance. In favour of this, it is reported about an anti-inflammatory action of *Costus speciosus* rhizome.¹⁸ It is more likely, the chemical reaction caused by the compounds in *Costus speciosus* leaf can unmask the insulin receptors in peripheral adipose tissues. With the correction of IR, the insulin level had also decreased. This can be explained by correction of the feedback mechanism in functioning beta cells. Elevated plasma insulin level is characteristic in IR and it is as a result of insulin deficiency in peripheral insulin sensitive tissues followed by over stimulation of the β cells for insulin production. In our study, both methanol and water extracts of *Costus speciosus* leaf demonstrated a significant insulin lowering effect in experimental IR rats and consequently corrected hyperinsulinemia. Therefore, we suggest that the IR reversing action of *Costus speciosus* leaf might be by correcting inflammatory action in adipocytes and thereby increasing the insulin binding affinity of the receptors. This automatically corrects the insulin deficiency in peripheral tissues leading to feedback controlled reduction in serum insulin level. Even though, *Costus speciosus* extracts had reduced the insulin levels to normal, there was no significant hypoglycemic effect seen in either of the two extracts within one month therapy. It is understood that, the correction of pathological changes in biological systems need time for reversal of the compensatory metabolic changes and reactions. Therefore with correction of IR we expect that, continuation of the same beyond one month would be effective, in reversing the compensatory changes possible in the enzymes such as glucose phosphatase, hexokinases, phosphofructokinase and glycogen synthases which would reinstate normal glucose levels. Semenkovich *et al* have reported that, increased TG levels are associated with the progression of IR.¹⁹ and the same were observed here. Also we found a reduction of TG by CSLmex at very early level. This can be explained in two possible mechanisms. *Costus speciosus* might have an effect on insulin mediated lipoprotein lipase enzyme induction of TG uptake to the adipose cells. In addition to that, *Costus speciosus* also would have inhibited the insulin mediated hormone sensitive lipase action and reduce TG breakdown in adipose cells. There is no available literature to compare the hypotriglyceridemic effect of on *Costus speciosus* leaf. Nevertheless, *Costus speciosus* rhizome hexane extract in a dose of 250 mg/kg has exemplified a TG lowering effect in diabetic rats.⁵ They have explained their effect by reducing the hormone sensitive lipase action which is favourable for our findings of CSLmex. They have expanded their work for extracted analysis and done with two compounds, Costunolide⁸ and Eremanthin⁹ extracted from *Costus speciosus* rhizome and found that both had significantly reduced triglyceride levels in diabetic rats after 60 days therapy. In conclusion, we would like to

emphasise that, both *Costus speciosus* leaf methanol and water extracts possesses a significant insulin sensitive effect in experimental rat models within four weeks. In addition, methanol extract has a significant hypotriglyceridemic effect. Therefore, we suggest future corresponding dose response studies to establish therapeutic and toxic doses of *Costus speciosus* leaf extracts against insulin resistance. Future studies are also possible for glucose metabolism and hepatic insulin resistance with long term therapy although, it is absent with one month treatment.

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