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Coriandrum sativum L. aqueous extract mitigates high fat diet induced insulin resistance by controlling visceral adiposity in C57BL/6J Mice

[Coriandrum sativum L. extracto acuoso mitiga dieta rica en grasas de alta resistencia a la insulina inducida por el control de la adiposidad visceral en ratones C57BL/6J]

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Abstract

This study investigates the effect of dietary supplementation with *Coriandrum sativum* L. seed aqueous extract (CS) to a high fat diet (HFD), for induced insulin resistance (IR) C57BL/6J mice. Changes in body weight, food intake, feed efficiency ratio, fasting blood glucose (FBG), plasma insulin, fasting insulin resistance index (FIRI), plasma and hepatic triglyceride (TG), total cholesterol (TC) and, plasma free fatty acid (FFA) levels were evaluated in control and treated groups. Also, the diameter, surface area and number of adipocytes and, intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin response test (IPRTT) were performed. CS supplementation (1% and 3% w/w) to HFD fed mice (for 12 weeks) significantly prevented HFD induced increment in body weight gain, food intake, feed efficiency, FBG, plasma insulin, FIRI, plasma and hepatic TG and TC and, plasma FFA, adipocyte diameter and surface area along with decrement in adipocyte number. Also, improved responses were recorded in the IPGTT and IPRTT in CS supplemented HFD fed mice. These set of changes were comparable to the rosiglitazone (0.05%) supplemented HFD fed mice. Our findings suggest that CS improves insulin sensitivity primarily by mitigating plasma and tissue lipids and, adipocyte hypertrophy.

Keywords: *Coriandrum Sativum* L., high fat diet, Insulin resistance, adipocyte hypertrophy

Resumen

En este estudio se investigó el efecto de un extracto acuoso de semillas de *Coriandrum sativum* L. (CS), adicionado a una dieta con alto contenido graso en ratones C57BL/6J, con resistencia a la insulina inducida. Los cambios en el aumento de peso corporal, consumo de alimento, eficiencia alimenticia, glicemia, insulina plasmática, índice de resistencia a la insulina, triglicéridos hepáticos y plasmáticos, colesterol total y concentración plasmática de ácidos grasos libres, fueron evaluados en grupos control y tratados. Adicionalmente se controló, el diámetro, superficie y número de adipocitos, prueba de tolerancia a la glucosa intraperitoneal y la prueba de respuesta de la insulina por vía intraperitoneal. La adición de CS (1% y 3% w / w) a la dieta con alto contenido graso a ratones (12 semanas) previno de manera significativa el incremento de peso, la ingesta de alimentos, la eficiencia alimenticia, FBG, la insulina plasmática, FIRI, los triglicéridos hepáticos y plasmáticos, el colesterol total, ácidos grasos libres plasmáticos, el diámetro de los adipocitos y la superficie junto con el decremento en el número de los adipocitos. Además, mejoras de la respuesta se registraron en el IPGTT y IPRTT. Este conjunto de cambios fue comparable al obtenido con rosiglitazona (0,05%), adicionada a la dieta con alto contenido graso. Estos hallazgos sugieren que el CS mejora la sensibilidad a la insulina principalmente por la mitigación de los lípidos del plasma, del tejido y la hipertrofia del adipocito.

Palabras Clave: Dieta rica en grasas, resistencia, a la insulina, hipertrofia de los adipocitos

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INTRODUCTION

Changes in lifestyle and intake of caloric rich diets have predisposed the populace to obesity. Type 2 diabetes (T2D) is also closely associated with obesity and is characterized by an insulin resistance (IR) severely affecting glucose disposal (Frőde and Medeiros, 2008). Treatment of IR involves popular lipid lowering and insulin sensitizing drugs that have been associated with many side effects. Multiple drug usage is the necessary option for maintaining glycaemic levels and other associated manifestation in T2D patients (Gerich, 2001). These compelling reasons provide impetus for investigating the medicinal properties of herbs for use as alternatives in the treatment of T2D on a global scale. In this context, World Health Organization (WHO) has estimated that, about 25% of modern medicines are derived from plants and that, the global market for herbal medicine currently stands at over 60 million US$ annually (WHO, 2009).

Coriandrum sativum L. (Apiaceae) (CS) is an annual herb, the fresh leaves and dried seeds of which form part of Middle Eastern, Mediterranean, Indian, Latin American, African and Southeast Asian cuisines. Decoction and tincture of powdered seeds of CS alone or in combination with other herbal agents are recommended for dyspeptic complaints, loss of appetite, convulsion, insomnia and anxiety (Grieve, 1971). It is also used as medication against diabetes, indigestion, flatulence, renal disorders and as a diuretic agent in India and Morocco (Grieve, 1971; Emamghoreishi *et al*., 2005). It is also used in urethritis, cystitis, urinary tract infection, urticaria, rashes, burns, sore throat, vomiting, indigestion, nosebleed, cough, allergies, hay fever, dizziness and amoebic dysentery (Grieve, 1971; PDR-HM, 2004).

Phytochemical constituents of CS seeds have been studied extensively and its analysis has revealed the presence of polyphenols (rutin, caffeic acid derivatives, ferulic acid, galic acid, and chlorogenic acid), flavonoids (quercetin and isoquercetin) and β-carotenoids (Melo *et al*., 2003). The essential oil obtained from CS seeds contains α and β- pinene, camphor, citronellol, coriandrol, *p*-cymene, geraniol, geranyl acetate, limonene, linalool, myrcene, α and β phellandrene and α and β-terpinene. Also many fatty acids have been identified in the seeds oil. A large number of water soluble compounds have been identified including monoterpenoid glycosides, monoterpenoid glucose sulfate and other glycosides (Sergeeva, 1975; Ishikawa *et al*., 2003). The pharmacological activities of various extracts and of the essential oil of CS seeds have been also studied. The essential oil has been found to possess antimicrobial (Baratta *et al*., 1998) and antifungal properties (Garg and Siddiqui, 1992). Its efficacy as a hypoglycemic (Gray and Flatt, 1999), hypolipidemic (Chithra and Leelamma, 1997; Chithra and Leelamma, 1999; Lal *et al*., 2004), hypocholesterolemic (Dhanapakiam *et al*., 2008), antihypertensive (Medhin *et al*., 1986), antioxidant (Melo *et al*., 2003; Ramadan *et al*., 2003; Bajpai *et al*., 2005), antimutagenic (Cortes-Eslava *et al*., 2004), anxiolytic (Emamghoreishi *et al*., 2005), antimicrobial (Kubo *et al*., 2004; Cantore *et al*., 2004), larvicidal (Consoli *et al*., 1988) and post-coital antifertility (Al-Said *et al*., 1987) agent have also been reported.

As CS has been used as traditional anti-diabetic herbal agent and it's hypoglycemic and insulin secretor effects have been evaluated in streptozotocin induced diabetic rats (Eidi *et al*., 2009; Swanston-Flatt *et al*., 1990), the present study was designed to assess the efficacy of aqueous extract of CS in alleviating IR in high fat diet fed model of T2D.

MATERIALS AND METHODS

Plant Extract

CS seeds were procured from local ayurvadic medicinal shop of Vadodara, India. Hundred grams of powdered seeds were boiled at 100°C for 3 hrs in distilled water. Resulting filtrate was concentrated in a hot air oven until it formed a semisolid paste, which was then freeze dried. The yield was 12% w/w. Two doses (1% and 3%) of aqueous extract of CS were mixed with high fat diet.

Experimental Animals

Male C57BL/6J mice (6-8 weeks of age) were purchased from the National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN), Hyderabad, INDIA. They were housed and maintained in clean polypropylene cages and fed with standard laboratory diet (SLD) and water *ad libitum*. The experiments were carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and approved by the animal ethical committee of the Department of Zoology, The Maharaja Sayajirao University of Baroda, Vadodara (Approval No.827/ac/04/CPCSEA) .

Experimental Design

30 animals were randomly allocated into 5 groups of 6 animals each. Mice were fed with standard laboratory diet (SLD) or high fat diet (HFD) for 12 weeks (Jadeja *et al*., 2010; Thounaojam *et al*., 2010). CS or Rosiglitazone (ROS) were given to the experimental animals by mixing with HFD.

Group I (SLD): Mice were fed with SLD
Group II (HFD): Mice were fed with HFD
Group III (HFD+CS1%): Mice fed with HFD containing CS extract (1% w/w)
Group IV (HFD+CS3%): Mice fed with HFD containing CS extract (3% w/w)
Group V (HFD+ROS): Mice fed with high fat diet containing Rosiglitazone (0.05% w/w).

At the end of the experimental period, blood was collected from retro orbital sinus in EDTA coated vial under mild ether anesthesia. Plasma was obtained by cold centrifugation (4°C) of the vials for 10 min at 3000 rpm. Later, animals were sacrificed by cervical dislocation and epididymal fat pad were excised, weighted and fixed in 4% buffered paraformaldehyde.

Body weight, food intake and feed efficiency

Known quantity of food (SLD or HFD) was given to the respective experimental groups and food intake was measured daily. Feed efficiency ratio (FER) was expressed as the total weight gain of an experimental animal during 12 weeks ÷ the total food intake.

Plasma and hepatic lipids

Plasma free fatty acid (FFA) content was estimated by the method of Itaya and Ui, (1965) while, triglyceride (TG) and total cholesterol (TC) contents were estimated by using enzymatic kits (Reckon Diagnostics. Ltd, Vadodara, India) in a semi autoanalyser (Micro lab 300 L, Merck). Total lipids were extracted from liver of control and experimental animals with chloroform: methanol (2:1) (Folch *et al*., 1957) and hepatic Free fatty acids were assayed in the same (Itaya and Ui, 1965). Known quantity of lipid extract was than dissolved in 1% Triton X-100 (Thounaojam *et al*., 2010) and TC and TG were assayed using above kits.

Blood glucose, plasma insulin and fasting insulin resistance index (FIRI)

Animals were fasted overnight (for 12 hrs) and later blood glucose was measured in whole blood sample obtained from tail vein (by one touch glucometer, Sugar Scan, HMD BIOMEDICAL INC., India). Plasma insulin was assayed using Mouse ELISA kit (Mercodia Developing Diagnostics Ltd, Sweden). Fasting insulin resistance index (FIRI) was expressed as: - Fasting insulin (pmol/l) x Fasting blood glucose (mg/dl) ÷ 25.

Intraperitoneal glucose tolerance test (IPGTT)

Fasting (12 hrs) blood glucose was measured in whole blood (by one touch glucometer, Sugar Scan, HMD BIOMEDICAL INC., India) obtained from tail vein (0 min). Later, glucose solution was injected intraperitoneally (2 g/kg) and blood glucose was assayed at 30, 60, 90 and 120 min and the tolerance curves plotted. Area under the curve ($AUC_{glucose}$) was calculated based on the trapezoid rule (Graph Pad Prism version 3.0).

Intraperitoneal insulin response test (IPIRT)

Overnight fasted mice received insulin (Aventis Pharma Deutschland GmbH, Mumbai, India) 0.2 U/kg body weight by intraperitoneally. Blood samples were collected from tail vein at 0 min (before administration) and subsequently at 10, 20, 30 and 60 min after administration of insulin. Blood glucose was measured in whole blood (by one touch glucometer, Sugar Scan, HMD BIOMEDICAL INC., India). K_{ITT} was determined with the formula: $K_{ITT}= 0.693\times100 \div T_{½}$. Where $T_{½}$ is half-life of plasma glucose decay was obtained with the formula: $T_{½}= \ln2 \div \omega$. Where, ω constant of plasma glucose disintegration was obtained with the formula: $\omega = \ln C1 - \ln C2 \div T2 - T1$ with glucose concentration C1 at time T1 (10 min) and C2 at T2 (60 min) (Thounaojam *et al*., 2010).

Histology of epididymal fat pad

Epididymal fat pad was fixed in 4% buffered paraformaldehyde, dehydrated in graded alcohol series and embedded in paraffin wax. Five µm sections were cut (by Leica RM 2115 Microtome) and stained with hematoxyline and eosin (H&E) and examined under Leica microscope. Photographs of adipocytes were taken with Canon power shot S7 digital Camera (400 X). To quantify adipocyte number and diameter, the H&E stained sections were analyzed using an image analysis system (Image Pro-Plus, Silver Spring, MD).

Statistical analysis

Statistical analysis of the data was done by one way ANOVA followed by Bonferroni's multiple

comparison test and results were expressed as mean ± S.E.M (Using Graph Pad Prism version 3.0 for Windows, Graph Pad Software, San Diego California USA).

RESULTS

Body weight gain and feed efficiency ratio

HFD group recorded significant increase in body weight gain but not in food intake and feed efficiency ratio as compared to SLD ($p<0.01$). HFD+CS (CS 1% & CS 3%) recorded significantly dose dependent decrement in body weight gain, food intake and feed efficiency ratio as compared to HFD fed mice (Table 1). HFD+ROS group also showed decrement of the said parameters which were comparable to HFD+CS1% but, HFD+CS3% was the most efficient in inducing.

Table 1. Effect of CS extract and Rosiglitazone on Body weight, Food intake and Feed efficiency ratio

	SLD	HFD	HFD+CS1%	HFD+CS3%	HFD+ROS
Initial body weight(g)	24.40±0.86	22.53±0.79	23.32±0.24	22.22±1.34	24.00±0.64
Final body weight(g)	29.00±0.70	32.42±0.28	30.32±0.30	25.50±1.12	31.16±0.59
Weight gain (g)	4.32±0.69	9.86±0.59^{c}	7.03±0.16^{B}	3.28±0.36^{C}	7.16±0.074^{B}
Food intake (g/day)	2.26±0.1979	3.72±0.4195^{a}	2.39±0.1234^{A}	1.88±0.1137^{B}	3.02±0.089^{NS}
Feed efficiency ratio	0.02±0.002	0.03±0.001^{b}	0.03±0.002^{NS}	0.02±0.002^{A}	0.02±0.002^{A}

Data are expressed as the mean ± S.E.M. Where, a) $p<0.05$, b) $p<0.01$, c) $p<0.001$ and ns: non significance when, SLD vs HFD. A) $p<0.05$, B) $p<0.01$, C) $p<0.001$ and NS: non significance when, HFD vs HFD+CS1%, HFD+CS3% and HFD+ROS

Plasma and hepatic lipid profile

Plasma and hepatic TC and TG levels and plasma FFA level were significantly elevated in HFD group as compared to SLD group ($p<0.01$). CS supplemented HFD fed groups (CS 1% & CS 3%) and HFD+ROS were significantly ($p<0.01$) able to attenuate the effect of HFD as was evident in form of decrement in levels of hepatic and plasma TC and TG and plasma FFA (Table 2).

Fasting blood glucose (FBG) and serum Insulin levels

FBG, plasma insulin level and FIRI were significantly higher in HFD group ($p<0.01$) as compared to SLD group. However, CS supplementation of HFD mice groups recorded significantly lowered levels of these parameters in dose dependent manner as compared to HFD group ($p<0.01$; Table 2).

Intraperitoneal glucose tolerance test and Intraperitoneal insulin response test

IPGTT of HFD fed mice recorded significant elevation in glucose level at 30 min that failed to return to its normal level at 120 min. $AUC_{glucose}$ of HFD fed mice was significantly higher compared to SLD mice ($p<0.01$). However, IPGTT of CS supplemented HFD mice showed dose dependent decrement in $AUC_{glucose}$ compared to that of HFD fed mice ($p<0.01$). HFD+ROS group also recorded a decrement in $AUC_{glucose}$ values compared to HFD group (Fig. 1).

IPIRT plots of glucose levels of HFD and SLD fed mice were comparable, however, CS supplemented HFD fed mice showed significant improvement in the IPIRT curves. The same was evident in the form of higher K_{ITT} values in these groups compared to the HFD group ($p<0.01$). HFD+ROS group also recorded higher K_{ITT} values of IPIRT as compared to HFD group (Fig. 2).

Table 2. Effect of CS extract and Rosiglitazone on plasma Glucose and serum Insulin

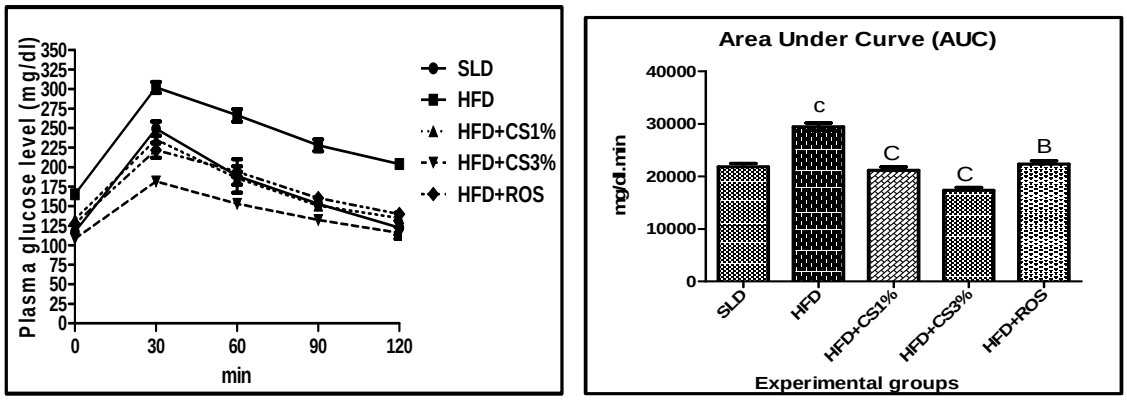
	SLD	HFD	HFD+CS1%	HFD+CS3%	HFD+ROS
Plasma					
TC(mg/dl)	68.50±10.56	142.70±7.63^{c}	103.00±7.0^{B}	74.80±8.23^{C}	81.25±11.09^{C}
TG(mg/dl)	50.00±5.22	152.30±20.67^{c}	102.30±9.24^{C}	76.50±4.85^{C}	70.25±11.69^{C}
FFA(mg/dl)	35.32±2.32	101.00±10.15^{c}	79.23±3.84^{NS}	37.97±2.08^{C}	50.28±3.70^{B}
Glucose(mg/dl)	110.00±5.21	162.80±3.47^{c}	131.30±10.71^{A}	117.00±8.31^{C}	128.00±4.35^{C}
Insulin(pmol/L)	38.89±3.81	79.00±4.34^{c}	56.43±2.96^{B}	44.97±4.44^{C}	46.70±3.41^{C}
FIRI	168.70±8.42	513.70±26.10^{c}	309.20±21.93^{C}	201.10±25.35^{C}	243.70±21.48^{C}
Liver					
TC(mg/dl)	17.23±2.34	50.75±7.33^{b}	34.75±5.07^{NS}	23.50±2.90^{B}	24.44±2.66^{B}
TG(mg/dl)	27.00±3.06	80.25±7.46^{c}	67.50±6.41^{NS}	33.65±5.49^{B}	44.25±4.34^{B}
Adipocyte					
Diameter(µm)	30.00±1.57	78.70±3.71^{c}	61.20±3.13^{B}	33.20±2.26^{C}	44.10±3.05^{C}
Surface area(µm^{2})	706.00±86	4862.00±125^{c}	2940.10±108^{B}	860.00±93^{C}	1520.60±122^{C}
Number(cells/1x10^{6} µm^{2})	941±81	177±76^{c}	580±66^{B}	864±62^{C}	748±75^{C}

Data are expressed as the mean ± S.E.M Where, $p<0.05$, b) $p<0.01$, c) $p<0.001$ and ns: non significance when, SLD vs HFD. A) $p<0.05$, B) $p<0.01$, C) $p<0.001$ and NS: non significance when, HFD vs HFD+CS1%, HFD+CS3% and HFD+ROS

Adipocyte diameter, number and surface area

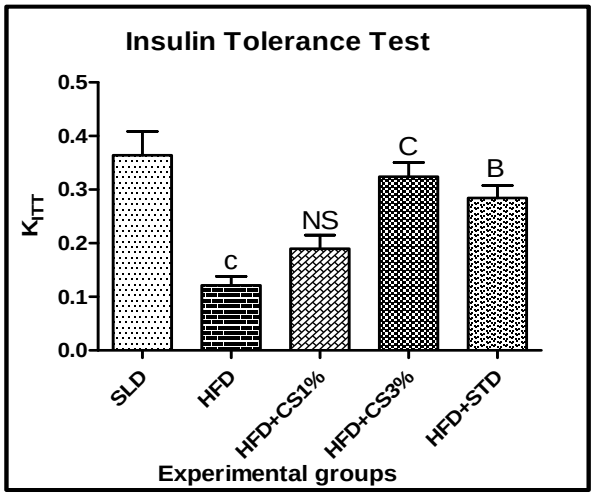
Microscopic examination of epididymal fat pad of HFD group recorded a significant increase in diameter and surface area of adipocytes compared to the adipocytes of SLD group ($p<0.01$). CS supplemented HFD groups showed adipocytes with mixed dimensions. However, the overall score of measurements of diameter and surface area of adipocytes recorded in HFD+CS (1% & 3%) were significantly lower than that of HFD group. The total number of adipocytes counted in a unit area in HFD+CS (1% & 3%) groups were significantly higher ($p<0.01$) than in the HFD group. These numbers were comparable to SLD or HFD+ROS groups (Table 2). HFD+ROS group also showed moderate decrement in diameter of adipocyte compared to HFD group.

Fig.1. Effect of CS extract and Rosiglitazone on IPGTT and AUC



Data are expressed as the mean ± S.E.M a) p<0.05, b) p<0.01, c) p<0.001 and ns: non significance when, SLD vs HFD. A) p<0.05, B) p<0.01, C) p<0.001 and NS: non significance when, HFD vs HFD+CS1%, HFD+CS3% and HFD+ROS

Fig.2. Effect of CS extract and Rosiglitazone on IPIRT and K_{ITT}



Data are expressed as the mean ± S.E.M a) p<0.05, b) p<0.01, c) p<0.001 and ns: non significance when, SLD vs HFD. A) p<0.05, B) p<0.01, C) p<0.001 and NS: non significance when, HFD vs HFD+CS1%, HFD+CS3% and HFD+ROS

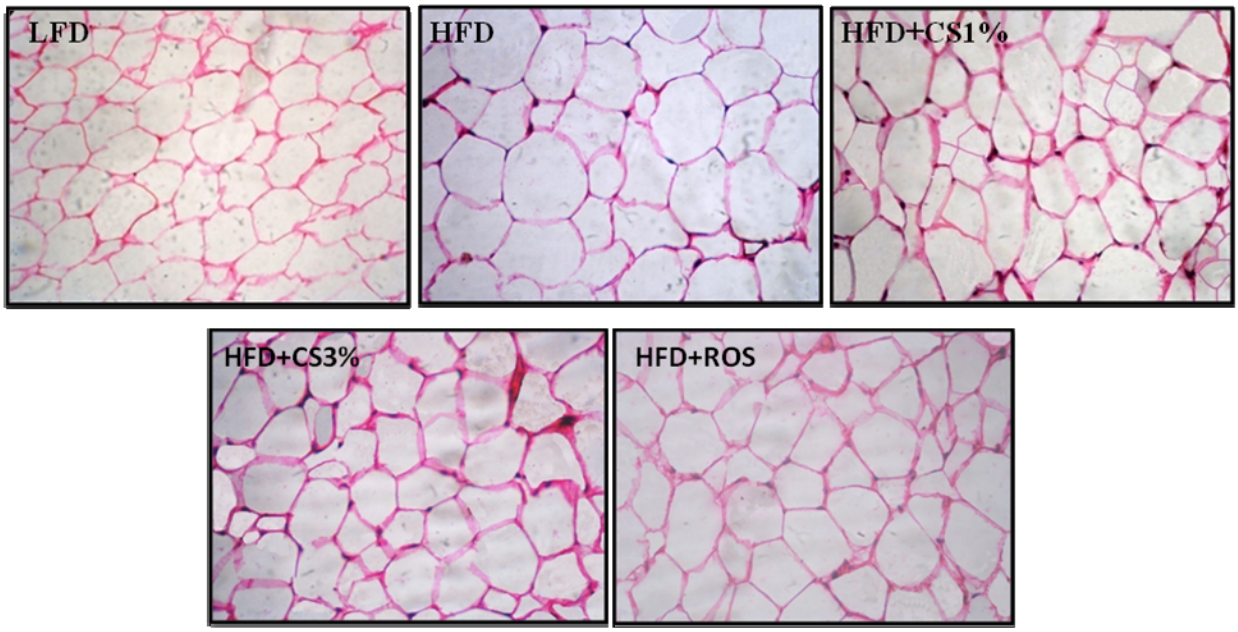
DISCUSSION

C57BL/6J mouse is a popular experimental model used in pre-clinical investigations of herbal and synthetic therapeutic agents against diabetes and obesity as there mice undergo a series of physiological changes when fed with high fat diet for 12-15 weeks. These changes are similar to the onset and progression of T2D and IR (Ahrén *et al*., 1997). In these mice, HFD induced IR is preceded by hyperlipidemia and visceral adiposity.

Our study has shown significant increment in body weight gain, food intake and feed efficiency ratio in HFD mice, well reflected in the form of significant increment in the weight of epididymal fat pad (personal communication). However, CS (1% & 3%) supplementation of HFD mice significantly prevented the characteristic body weight gain and increase in epididymal fat pad mass possibly due to decreased food intake. Previous studies have reported that insulin sensitivity in T2D patients improved with weight loss (DeFronzo and Ferrannini, 1991). CS supplemented HFD fed mice minimized the increase in hepatic and plasma TC and TG levels characteristic of HFD. These observations are in accordance with a previous report of Chithra and Leelamma (1997) on CS induced decrement in lipid profile of *Sprauge dawly* rats maintained on a hyperlipidemic diet. It has been reported that, increase in circulating level of plasma

FFA contributes to an increase in IR and inhibition of glucose uptake by skeletal muscles and other peripheral tissues (Boden *et al*., 1997). Also, in ob/ob mice, hyperinsulinemia develops due to decreased sensitivity towards insulin in liver, muscle and adipose tissues (Genuth *et al*., 1971). CS supplemented HFD mice (1% & 3%) were able to improve IR by decreasing levels of plasma FFA and insulin titer. Also, an improvement in fasting plasma glucose levels and FIRI values provide ample testimony to CS induced improvement of IR in HFD fed mice. IPGTT and IPIRT tests were carried out in control and experimental mice to assess CS induced possible improvement in insulin sensitivity and the results obtained were compared with HFD group. Lower $AUC_{glucose}$ values and higher K_{ITT} indices recorded in HFD+CS (1% & 3%) groups are attributable to improved insulin sensitivity in CS supplemented HFD fed mice. These mitigating changes are comparable to ROS induced changes in visceral adiposity and IR.

Figure 3. Photomicrograph of Epididymal fat pad showing the effect of CS extract and Rosiglitazone on adipocyte morphology



The histological manifested changes in adipocyte mass and size of HFD are attributable to diet induced lipogenesis. Co-presence of CS in HFD is able to resist the adiposity changes caused due to fat rich diet. Adipocyte hypertrophy is a strong evidence of visceral obesity and IR (Flier, 2004; Wellen and Hotamisligil, 2005) and in fact, the larger adipocytes are associated with IR and smaller ones with better insulin sensitivity (Okuno *et al*., 1998; Kubota *et al*., 1999; Kodowaki, 2000). The sizes of adipocytes in HFD and HFD+CS groups of mice in this context could easily reflect the higher IR in the former and greater insulin sensitivity in the later. The observations on adipocyte number and size in HFD+CS (1%) and HFD+CS (3%) also tend to suggest the dose dependent favorable influence of the extract in preventing diet induced visceral adiposity and IR.

The observed significant anti-hyperglycemic effect of CS extracts might also suggest increased peripheral glucose uptake as well as decreased transport of glucose across the intestinal epithelium (Gallagher *et al*., 2003). *In vivo* studies on this line and the possible role of CS extract to regulate the expression of PPARγ and other related genes in HFD mice are in progress.

CONCLUSION

This inventory is however first report that has investigated role of CS extract in improvement of HFD induced IR. These results are attributable to multiple physiological processes such as CS extract induced decrement in food intake, lowering of plasma and tissue lipids and decrement in size of adipocytes. Also, CS extract induced lowering of insulin, eventually leading to improvement of IR, improved insulin sensitivity and efficient clearance of glucose load, further corroborate these observations. Since, protective role of CS extract against STZ induced type

I diabetes has already been established, this study is an addition to its already established pharmacotherapeutic uses.

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