DOI: 10.7860/JCDR/2017/23910.9864

Original Article

Pharmacology Section

Anti-Atherosclerotic Potential of Aqueous Extract of *Cinnamomum zeylanicum* Bark against Glucocorticoid Induced Atherosclerosis in Wistar Rats

IM NAGENDRA NAYAK[1], RAJASEKHAR CHINTA[2], RAGHU JETTI[3]

ABSTRACT

Introduction: Atherosclerosis is one of the major causes of disability of blood vessels which can result in development of many cardiovascular disorders. There is a strong association between atherosclerosis and insulin resistance and dyslipidemia.

Aim: To study the anti-atherosclerotic potential of *C. zeylanicum* bark extract in insulin resistance associated atherosclerosis and worsened Atherogenic Index (AI) associated with dyslipidemia, which are the predominant complications of steroid diabetes in Wistar rats.

Materials and Methods: A sum of 36 rats were categorized into five study groups and one plain control. In a 12 day study period, respective drug treatments were given every day throughout the study period whereas, dexamethasone dosage was started from day seven onwards. On day 12, fasting blood samples were collected and processed for lipid estimation and the determined values were also used to assess AI further. Animals were sacrificed under ether anaesthesia and the aorta was dissected away for its measurement and histopathological findings. One-way ANOVA was used to analyse the data and multiple comparison was done, interpreted based on Post-Hoc Scheffe test.

Results: High dose of dexamethasone (8 mg/kg/i.p) in Dexa Control (DC) group produced significant dyslipidemia, increased risk of atherogenicity ($p<0.05$) and caused severe thickening (78.5% compared to Plain Control (PC) of wall of aorta. Rosiglitazone (ROSI) (8 mg/kg and 16 mg/kg) and *C. zelanicum* (CZE) extract treatments (500 mg/kg and 250 mg/kg) significantly prevented dyslipidemia, well maintained AI compared to dexa control ($p<0.05$). However, both the CZE treatments protected the aorta from atherosclerosis (40.3% and 30.2% compared to DC) and significantly prevented the dyslipidemia and reduced the risk of atherogenicity compared to ROSI treatment ($p<0.05$). Although, the CZE did not show difference in significance in maintaining very low density lipoprotein when compared to ROSI ($p>0.05$). The atherosclerotic changes were completely absent in both the CZE treatments whereas, ROSI treatments did not prevented the atherosclerosis of aorta completely as they showed moderate and mild atherosclerotic changes in the aorta.

Conclusion: The aqueous extract of *C. zelanicum* bark exhibited marked protection against dexamethasone induced atherosclerosis and also minimized the atherogenic risk in Wistar rats.

Keywords: Atherogenic index, Arteriosclerosis, Dexamethasone, Dyslipidemia

INTRODUCTION

Atherosclerosis is a multifactorial disease of arteries and a cause of many cardiovascular complications. It is generally characterized by increased size, endothelial dysfunction and vascular inflammation [1]. It commonly coexists with pro-atherogenic disorders. Considerable evidence is available to support the association between vascular disease and steroid induced insulin resistance [2]. By looking into clinical histories and autopsies, few researchers identified the association between obesity, hypertension, abnormal glucose metabolism and existence of atherosclerosis [3]. The lipoprotein lipase levels are also reduced with insulin resistance and results in decrease of VLDL clearance, which may make a smaller contribution to elevated TGs in this setting. Further, VLDL is metabolized to remnant lipoprotein and LDL, increased concentration of triglyceride rich VLDL particles contribute to abnormal HDL metabolism in insulin resistance condition and are strongly associated with atherosclerotic risk [4]. The cell organelle may undergo stress due to nutrients excess and that results in the development of atherosclerosis and insulin resistance. Disruption of homeostasis may occur at cell organelle that may result into ER and genomic stress due to excess glucose delivery. The factors affecting nuclear genome are oxidative stress and also due to accumulation of lipids inside the cells. They disrupt protective mechanisms that minimize the damage due to inflammation [5].

Glucocorticoids (GCs) are the key hormones that regulate glucose homeostasis and it is released in response to stress and low blood-glucose concentration. Excess of GC causes insulin resistance [6] and prolonged corticosteroid therapy accelerates the development of atherosclerosis [7]. Dexamethasone is a potent glucocorticoid, has high affinity for glucocorticoid receptors with minimal mineralocorticoid property. Several authors tried variable doses of dexamethasone to induce insulin resistance in rodents [8,9]. Dexamethasone treatment can also induce dose dependent changes in aorta as moderate and severe thickening of tunica media was observed in respective doses of 4 and 8 mg/kg dexamethasone [10].

Cinnamomum zeylanicum, a day to day routine spice and condiment in India, has been positively tested recently in type 2 diabetics for its anti-diabetic effect. It is also known for enhancing insulin sensitization in order to increase glucose uptake [11]. Methyl Hydroxyl Chalcone Polymer (MHCP) and cinnamaldehyde present in the extract of *C. zeylanicum* closely mimics insulin activity [12,13] and also few studies on its bark extract was in support of its potent hypolipidaemic activity in Streptozotocin (STZ) induced diabetic rats [14]. However, the effect of *C. zeylanicum* bark extract on dexamethasone induced atherosclerosis and risk of atherogenesis is yet to be evaluated.

The current study is part of the previously conducted study in which the preventive effects of CZE were evaluated against dexamethasone induced insulin resistance [11], and now it is intended to evaluate the anti-atherosclerotic potential of aqueous extract of *C. zeylanicum* bark against dexamethasone induced dyslipidemia and atherosclerosis in rats.

MATERIALS AND METHODS

This experimental study was carried out at Department of Pharmacology, KS Hegde Medical Academy, Mangalore, Karnataka, India, from August 2013 to January 2014.

Experimental Animals

A sum of 36 healthy male Wistar albino rats, weighing around 230-270 gm were chosen for this study. The animals were housed at 22-24°C temperature and maintained under 12 hour light -12 hour dark cycle for two weeks *ad libitum*. An approval from IAEC was obtained (Letter no: AEC/29//2011) prior to the study. All the procedures in this study were performed as per the CPCSEA revised guidelines.

Grouping

Animals were equally allocated into five treatment groups and one plain control with six animals in each [Table/Fig-1].

Sl. No	Groups
I	Plain control (PC)
II	Dexa control (DC)
III	Dexa+ ROSI 8 mg/kg
IV	Dexa+ ROSI 16 mg/kg
V	Dexa+ CZE 250 mg/kg
VI	Dexa+ CZE 500 mg/kg

[Table/Fig-1]: Grouping of animals (n=6).
Note: Dexa- Dexamethasone, ROSI-Rosiglitazone, *CZE- C.zeylanicum* bark extract

Plant Material and Extraction

Cinnamon (*C.zeylanicum*) bark was procured from SDM Ayurvedic pharmacy, Udupi, Karnataka in Dec 2013. The bark was dried, grinded, finely powdered and then subjected to multiple cycles of extraction in Soxhlet apparatus using distilled water at 80°C temperature. In each cycle, 50 gm of bark powder was packed and placed inside the Soxhlet chamber. The yield was concentrated by using rotary evaporator at reduced pressure [14]. A final yield of 6.1% extract was collected and stored in desiccator and used during this study [11].

Drugs and Doses

The doses were selected based on a pilot study that was conducted in a small group of animals.

Aqueous extract solution of *C. zeylanicum* (CZE) was prepared as 250 mg/ml and 500 mg/ml concentrations with distilled water. Group V and VI received 250 mg/kg and 500 mg/kg respectively. Rosiglitazone was procured from Sigma labs in a dry powdered form and it was suspended in 2% gum acacia solution. Nearly, 8 mg/kg and 16 mg/kg doses were advised orally to group III and IV respectively. However, dexamethasone injection 8 mg/kg body weight/day (intraperitoneal injection) was used in respective groups [11].

Study Procedure

The above mentioned doses of CZE and ROSI were administered everyday throughout the study period (12 days). Dexamethasone is long acting and highly potent steroid over others and devoid of mineralocorticoid activity [15,16]. However, dexamethasone treatment was initiated on day 7 and continued till last day of the study period. Each rat in each group was allowed to have 100gm of standard food pellets and 100 ml of water. On day 11, all the rats were fasted overnight and accessed water alone. The very next morning, respective drugs were administered to all groups two hours before collecting blood samples. All the blood samples were collected by puncturing retro orbital plexus under either anaesthesia and were centrifuged at 4000 rpm/20 min. The serum was separated from the sediment and processed for the estimation of lipid profile.

Estimation of Serum Lipids

The lipid profile was determined by using standard laboratory reagents and automatic analyser. The HDL cholesterol was determined by phosphotungstate magnesium acetate precipitation method, TGs were determined by GPO-PAP method and the serum total CH was determined by oxidase peroxidase method [17].

The VLDL and LDL were determined by using standard formulae which follows as:

VLDL= Triglycerides/5 and LDL= Total cholesterol – (HDL cholesterol – Triglycerides/5) respectively.

Atherogenic Index

The Atherogenic index is used to understand and assess the risk of development of atherogenicity in vessels. As the AI value rises the risk of atherogenesis also increases. It was employed and calculated in respective study groups by using the following formula [17].

- Atherogenic index (AI) = Total CH- HDL-C/HDL-C

Isolation of Aorta for the Histopathological Examination

Following the collection of fasting blood samples, rats were sacrificed by cervical dislocation. On ventral position the chest of the animal was opened with incision, aorta was traced and a distance of 2 cm was dissected away. Isolated tissues were fixed in 10% formalin and were employed for further histopathological observations. Sections were made 5 µm thick and stained with Haematoxylin and Eosin (H&E stain) and were observed for atherogenic/atherosclerotic changes in the aorta [18].

Measurement of Thickness of Aorta

The aortic sections were studied under 400X under Olympus photographic microscope and photomicrographs were captured. The thickness of the aorta in the photomicrographs was measured with the help of Image J 1.41o version [18].

Percent (%) difference in the thickness of aorta was calculated among study groups compared to PC by using following formula.

$$\% \text{ difference from PC} = \frac{PC - SG}{PC} \times 100$$

Note: PC-Plain control; SG- Study group (DC, CZE, ROSI)

Percent (%) difference in the thickness of aorta was calculated in treatment groups compared to DC by using following formula.

$$\% \text{ difference in the thickness of aorta from DC} = \frac{DC - TG}{DC} \times 100$$

Note: DC-dexa control; TG- treatment group (CZE, ROSI)

STATISTICAL ANALYSIS

Suitable data was represented as Mean±S.D. The statistical analyses were performed using One-way ANOVA followed by Dunnet post-Hoc test. Statistical significance was assumed at the 5% level of significance and $p<0.05$ was considered as significant.

RESULTS

Effect of CZE and ROSI on Serum lipids

In present study, treatment with high dose of dexamethasone (8 mg/kg i.p) caused significant fall in High Density Lipoproteins (HDL) levels and significantly raised TG, total CH, LDL and VLDL ($p<0.05$). Whereas, CZE 500 mg/kg treatment significantly elevated HDL levels compared to DC and both 8 mg/kg and 16 mg/kg of ROSI treated groups. CZE 500 mg/kg caused marked fall in LDL, VLDL,

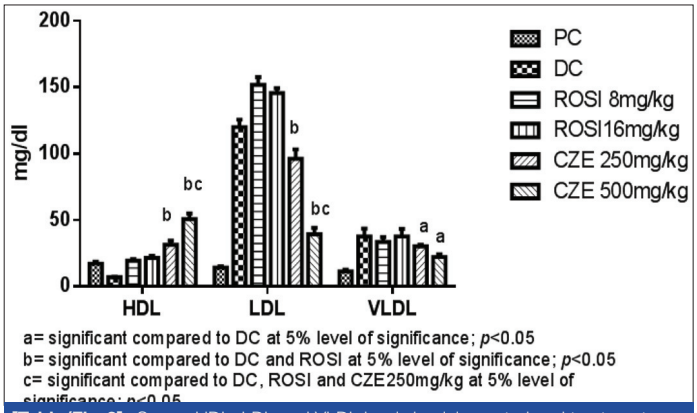
TG and CH levels compared to DC and both the ROSI treatments (p<0.05). However, there was no significant difference observed between CZE 250 mg/kg and 500 mg/kg treatments in reducing VLDL alone (p>0.05). Both the ROSI treatments (8 mg/kg and 16 mg/kg) improved serum HDL markedly compared to DC (p<0.05). Although, there was no significant difference between both ROSI treatments in reducing LDL, VLDL, TG and CH and raised HDL levels (p>0.05) [Table/Fig-2,3].

Effect of CZE and ROSI on Atherogenic index (AI)

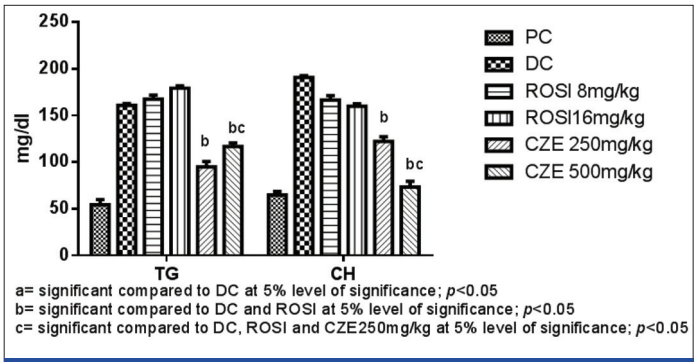
Dexamethasone significantly raised the AI compared to PC group and CZE 500 mg/kg significantly prevented the escalation of AI compared to DC and both the doses of ROSI treatment (p<0.05). Both 8 mg/kg and 16 mg/kg ROSI significantly prevented the rise in AI compared to DC alone. However, there was no significant difference between these doses (p>0.05) [Table/Fig-4].

Percentage Difference in the Thickness of Aorta among Study Groups from PC

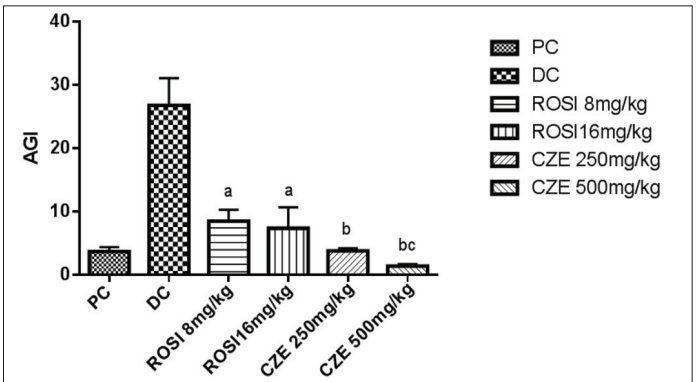
The aorta in dexamethasone treated group thickened by 78.5% whereas, ROSI 8 mg/kg and 16 mg/kg groups showed 34.2% and 54% thickness respectively. CZE 250 mg/kg group exhibited 24.4% increase in thickness of aorta and least percent increase in thickness observed in CZE 500 mg/kg with 6.4% compared to PC group [Table/Fig-5].



[Table/Fig-2]: Serum HDL, LDL and VLDL levels in plain control and treatment groups.



[Table/Fig-3]: Serum TG and CH levels in plain control and treatment groups.



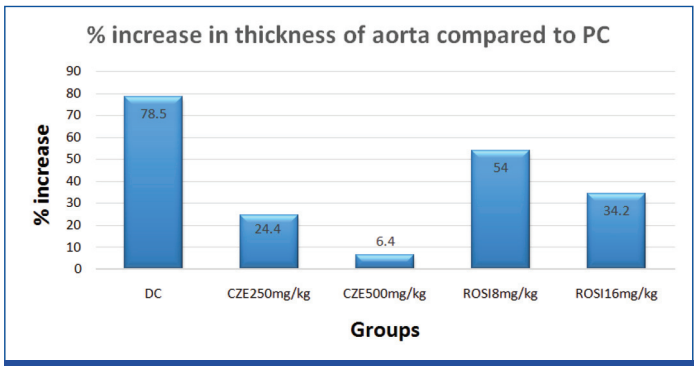
[Table/Fig-4]: Atherogenic index (AGI) in plain control and treatment groups.

Percentage Difference in the Thickness of Aorta among CZE and ROSI Treatment Groups from DC

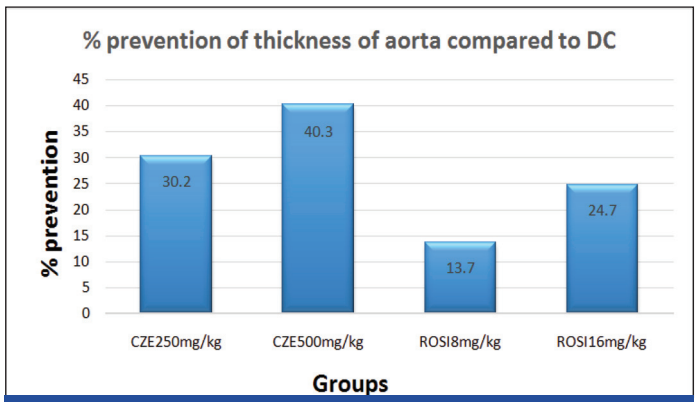
CZE 500 mg/kg effectively prevented the development of thickness of the aorta at maximum of 40.3% followed by CZE 250 mg/kg (30.2%) from DC group. ROSI 8mg/kg and 16mg/kg prevented the increase in thickness of aorta by 13.7% and 24.7% respectively from DC [Table/Fig-6].

Histopathological Findings

All sections of aorta of all groups were observed for the atherosclerotic changes and they were graded as mild, moderate and severe [Table/Fig-7]. The sections were observed under microscope with 400X magnification. Morphologically large sized artery consisting of inner tunica intima, middle tunica media and outer tunica adventitia. The tunica intima is lined by endothelial cells. The tunica media consisting of smooth muscle cells with elastic fibres with moderate thickening. The tunica adventitia is composed of loose connective tissue [Table/Fig-8a-e].



[Table/Fig-5]: Percentage increase in thickness of aorta in study groups compared to Plain Control (PC).



[Table/Fig-6]: Percentage difference in thickness of the aorta in study groups compared to Dexa Control (DC).

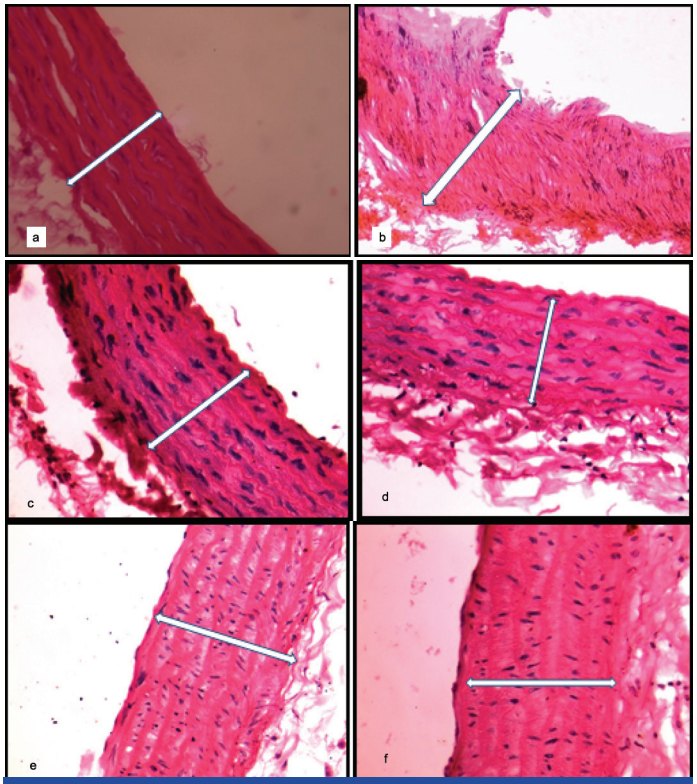
Group n=6	Atherosclerotic changes
PC	-
DC	+++
ROSI 8 mg/kg	++
ROSI 16 mg/kg	+
CZE 250 mg/kg	-
CZE 500 mg/kg	-

[Table/Fig-7]: Interpretation of histopathological changes in the aorta on day 12 in study groups.
Note: ('-'= Absent, '+'= Mild. '++'= Moderate, '+++'= Severe)

DISCUSSION

Several studies on dexamethasone induced insulin resistance model have also suggested the possible role of it in inducing dyslipidemia

[19]. The current study is also in accordance with above mentioned statement as the rats developed marked dyslipidemia with 8 mg/kg of dexamethasone dosing for six days. In addition, this study focused on effects of steroid induced dyslipidemia on AI, an index to assess risk of atherogenicity, Cardiac Risk Ratio (CRR) and atherosclerotic changes in the vasculature of the aorta.



[Table/Fig-8]: Photomicrographs of rats aorta captured under 400X magnification, Scale bar: 20 µm, H&E stain; a) Plain control (PC), normal aorta; b) Dexa control (dexamethasone 8 mg/kg) (DC) showing severe thickening of wall of aorta; c) CZE 250 mg/kg+ Dexamethasone 8 mg/kg showing normal appearance of wall of aorta; d) CZE 500 mg/kg+ Dexamethasone 8 mg/kg showing normal appearance of wall of aorta; e) ROSI 8 mg/kg+ Dexamethasone 8 mg/kg showing moderate thickening of wall of aorta; f) ROSI 16 mg/kg+ Dexamethasone 8 mg/kg showing mild thickening of wall of aorta.

The data in this study revealed that the high dose of dexamethasone (8 mg/kg) significantly raised the AI as compared to control that may increase the risk of atherogenicity. CZE treatment proven its potential in preventing rise in AI compared to ROSI pre-treatment. It also prevented dyslipidemia evidenced by increased HDL and dampened TG, CH and LDL levels markedly against dexamethasone treatment. Microphotographs studied in CZE groups showed normal pattern of morphological architecture with no atherosclerotic changes. In CZE 500 mg/kg, the thickness of the aorta in the images [Table/Fig-8d] showed minimum of 6.4% increase compared to PC and prevented thickening of aorta maximum of 40.3% compared to DC. In this study, CZE treatments has proven its efficacy in preventing dyslipidemia, rise of AI and atherosclerotic change of aorta over both doses of ROSI treatment.

The lipid lowering effects of CZE in this study are in accordance with the review by Bandara T et al., as low lipid levels are associated with increased adiponectin levels [20]. A study by Wei Z et al., postulated that, treatment for four weeks with cinnmaldehyde, a major constituent form the *C. zeylanicum* has a role in markedly reducing blood levels of TG and LDL, and enhanced HDL and the LDL levels are much lower than MET treatment [21]. Besides, a study by Mahmood S et al., supports the above finding by stating that, administration of 20 mg/kg cinnamaldehyde reduces HbA1C, serum CH and TG levels markedly [22]. In present study, the findings are corresponding to the above mentioned. In support, a clinical trial by Khan A et al., found the improved lipoproteins in people with Type II DM [23]. In addition, 200 mg/kg of Cinnamon markedly reduced the levels of CH, TG and increased HDL-C compared to active control groups [24]. Ciftci M et al., put forward that administration of various concentrations of cinnamon oil reduced CH in chickens due to its hypolipidemic and anti-oxidative properties, and also polyunsaturated fatty acid ratio increased [25,26]. Interestingly, CZE treatment did not show marked effect in reducing VLDL compared to ROSI suggesting its minimal role in maintaining VLDL. This finding is supported by the work done by Sharafeldin K et al., [27]. With all above, it is coherent that the cinnamaldehyde, the main constituent might be responsible for hypolipidemic effects of CZE. Whereas, the beneficial effects of CZE in reducing risk of atherogenesis can be attributed to its positive effect on HDL cholesterol against dexamethasone treatment.

Dramatically, no atherosclerosis of aorta was noted with CZE treatment, possibly due to presence of abundant HDL and compensatory reduction in LDL levels and their peroxidation. It also has the action of inhibiting copper mediated LDL oxidation and Cholesteryl Ester Transfer Protein (CETP). As postulated by Jarvill-Taylor KJ et al., It is believed that the MHCP which claims its insulin mimetic property also may play crucial role in preventing atherosclerosis probably by reducing glucose uptake and increasing peripheral glucose uptake into cells. It also increases the glycogen synthesis primarily in the liver and muscle tissue [12]. These insulin sensitizing actions of MHCP could also be helpful in preventing the elevation of serum lipids and atherosclerosis. The favourable effects of CZE against steroid induced atherosclerosis could also be attributed to its strongest action against advanced glycation end products and anti-oxidant activity [28]. The elasticity and relaxation of arterial smooth muscle were well maintained with CZE treatment probably by release of Endothelium-Derived Relaxing Factor (EDRF) upon stimulation by Ach from tunica intima [29]. Further, CZE treatment markedly elevated HDL-C in rats, and might have prevented the steroid induced atherosclerosis [30]. Additionally, CZE treatment could have been supported in the maintenance of integrity of the vessel wall by inhibiting endothelin-1 which plays a key role in thickening of the vessel wall in insulin resistance like condition [31]. The CZE was employed and compared for its preventive effects with an insulin sensitizer like rosiglitazone in order to understand its role in steroid diabetes associated complications like dyslipidemia and atherosclerosis.

LIMITATION

The lipid lowering effect and anti-atherogenesis property was not compared with any other hypolipidemic agents.

CONCLUSION

To conclude, high dose of dexamethasone increases the risk of atherogenicity in blood vessels which can precede by their sclerosis evidenced by increased thickness of the aorta. However, the aqueous extract of *C.zeylanicum* bark extract has the potential to prevent steroid induced rise in atherogenic index and sclerosis of vessels in Wistar rats. Further, the effects of the active constituents' cinnamaldehyde and MHCP have to be evaluated further for their efficacy and safety to develop them as a future agents, that are helpful in diabetes associated dislipidemia and also to prevent the sclerosis of blood vessels.

ABBREVIATIONS

TG- Triglycerides
HDL- High Density Lipoprotein
LDL- Low Density Lipoprotein
VLDL- Very Low Density Lipoprotein
ER- Endoplasmic Reticulam
GC- Glucocorticoid
Ach- Acetylcholine
CH- Cholesterol

REFERENCES

[1] Semenkovich CF. Insulin resistance and atherosclerosis. J Clin Invest. 2006;116(7):1813-22.
[2] Thent ZC, Lin TS, Das S, Zakaria Z. Histological changes in the heart and the proximal aorta in experimental diabetic rats fed with Piper sarmentsoum. Afr J Tradit Complement Altern Med. 2012;9(3):396-404.
[3] Enzi G, Busetto L, Inelmen EM, Coin A, Sergi G. Historical perspective: visceral obesity and related comorbidity in Joannes Baptista Morgagni's 'De sedibus et causis morborum per anatomen indagata. Int J Obes Relat Metab Disord. 2003;27(4):534-35.
[4] Ginsberg HN. Review: efficacy and mechanisms of action of statins in the treatment of diabetic dyslipidemia. J. Clin Endocrinol Metab. 2006;91(2):383-92.
[5] Han S, Liang CP, DeVries-Seimon, T Ranalletta M, Welch CL, Collins-Fletcher K, et al. Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions. Cell Metab. 2006;3(4):257-66.
[6] Bernal-Mizrachi C, Xiaozhong L, Yin L, Knutsen RH, Howard MJ, Arends JJ, et al. An afferent vagal nerve pathway links hepatic PPARα activation to glucocorticoid-induced insulin resistance and hypertension. Cell Metab. 2007;5(2):91-102.
[7] David JN. Is atherosclerosis a complication of long-term corticosteroid treatment? Am J Med. 1986;80(5):925-29.
[8] Korach Andre M, Gao J, Gounarides J, Deacon R, Islam A, Laurent D. Relationship between visceral adiposity and intramyocellular lipid content in two models of insulin resistance. Am J Physiol Endocrinol Metab. 2005;288(1):E106-16.
[9] Okumura S, Takeda N, Takami K, Yoshino K, Hattori J, Nakashima K, et al. Effects of troglitazone on dexamethasone-induced insulin resistance in rats. Metabolism. 1998;47(3):351-54.
[10] Hemanth KV, Nagendranayak IM, Huigol SV, Yendigeri SM, Narendar K, Rajasekhar CH. Dose dependent hepatic and endothelial changes in rats treated with dexamethasone. J Clin Diag Res. 2015;9(5):FF08-10.
[11] Rajasekhar Ch, Nagendranayak IM, Kokila BN, Rao UK, Vijayaraghavan S. Quantification and comparison of insulin sensitizing property of aqueous extract of Cinnamomum zeylanicum bark with rosiglitazone in steroid induced insulin resistance in wistar rats. J Chem Pharm Res. 2016;8(1):32-39.
[12] Jarvill-Taylor KJ, Anderson RA, Anderson DJ. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 Adipocytes. J Am Col Nutr. 2001;20(4):327-36.
[13] Anand P, Murali KY, Tandon V, Murthy PS, Chandra R. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chemico-Biological Interactions. 2010;186:72-81.
[14] Syed AH, Ritu B, Nair MS, Syed SH. Aqueous bark extract of Cinnamomum zeylanicum: A potential therapeutic agent for streptozotocin-induced type 1 diabetes mellitus (T1DM) rats. Tro J of Pharma Research. 2012;11(3):429-35.
[15] Zoorob RJ, Cender D. A different look at corticosteroids. Am Fam Physician. 1998;58(2):443-50.
[16] Blevins LS. Cushing's syndrome. Massachusetts: Kluwer Academic Publishers; 2005. pp. 107.
[17] Hassan S, El-Twab SA, Hetta M, Mahmoud B. Improvement of lipid profile and antioxidant of hypercholesterolemic albino rats by polysaccharides extracted from the green alga Ulva lactuca Linnaeus. Saudi J Biol Sci. 2011;18(4):333-40.
[18] Chek k, Eddie HT, Luo B, Huang CL, Loo JS, Choong C, et al. SMAD3 deficiency promotes inflammatory aortic aneurysms in angiotensin II infused mice via activation of iNOS. J Am Heart Ass. 2013;2:e000269.
[19] Nethrakere C, Nagendranayak IM, Vinodraj K, Bhat NGM, Paul M, Dasaraju R, et al. Comparison of the efficacy of clove (syzygium aromaticum) oil with pioglitazone on dexamethasone induced hepatic steatosis, dyslipidemia and hyperglycaemia in albino rats. J Clin Exp Res. 2015;3(1):169-73.
[20] Bandara T, Uluwaduge I, Jansz R. Bioactivity of cinnamon with sepecial emphasis on diabetes mellitus: A review. Int J Food Nutr. 2012;63(3):380-86.
[21] Wei Z, Yan-cheng Xu, Fang-jian GUO, Meng YE, Meng-li LI. Anti-diabetic effects of cinnamaldehyde and berberine and their impacts on retinol-binding protein-4 expression in rats with type 2 diabetes mellitus. Chin Med J. 2008;121(21):2124-28.
[22] Mahmood S, Talat A, Karim S, Khurshid R, Zia A. Effect of cinnamon extract on blood glucose level and lipid profile in alloxon induced diabetic rats. Pak J physiol. 2011;7(1):13-16.
[23] Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon Improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003;26(12):3215–18.
[24] Ismail NS. Protective effects of aqueous extracts of cinnamon and ginger herbs against obesity and diabetes in obese diabetic rats. W J Dairy Food Sci. 2014;9(2):145-53.
[25] Ciftci M, Simsek UG, Yuce A, Yilmaz, O, Dalkilic B. Effects of dietary antibiotic and cinnamon oil supplementation on antioxidant enzyme activities, cholesterol levels and fatty acid compositions of serum and meat in broiler chickens. Acta Veterinaria Brno. 2010;79(1):33-40.
[26] Lee JS, Jeon SM, Park EM, Huh TL, Kwon OS, Lee MK, et al. Cinnamate supplementation enhances hepatic lipid metabolism and antioxidant defense systems in high cholesterol-fed rats. J Med Food. 2003;6(3):183-91.
[27] Sharafeldin K, Rizvi MR. Effect of traditional plant medicines (*Cinnamomum zeylanicum* and *Syzygium cumuni*) on oxidative stress and insulin resistance in streptozotocin-induced diabetic rats. J Basic App Zoo. 2015;72:126-34.
[28] Jin Seori, Cho KH. Water extracts of cinnamon and clove exhibits potent inhibition of protein glycation and anti-atherosclerotic activity in vitro and in vivo hypolipidemic activity in zebrafish. Food Chem Toxi. 2011;49(7):1521-29.
[29] Blaise GA, Stewart DJ, Guérard MJ. Acetylcholine stimulates release of Endothelium-derived relaxing factor in coronary arteries of human organ donors. Can J Cardiol. 1993;9(9):813-20.
[30] Zeiher AM, Sahachinger V, Hohnloser SH, Saubier B, Just H. Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated High-Density Lipoprotein levels ameliorate abnormal vasoconstriction in early atherosclerosis. Circulation. 1994;89(6):2525-32.
[31] Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. J Clin Endocrinol Metab. 2001;86(10):4666-73.

PARTICULARS OF CONTRIBUTORS:
1. Professor and HOD, Department of Pharmacology, Mount Zion Medical College, Adoor, Kerala, India.
2. Senior Grade Lecturer, Department of Pharmacology, Melaka Manipal Medical College, Manipal University, Manipal, Karnataka, India.
3. Assistant Professor, Department of Basic Medical Sciences, College of Applied Medical Sciences, King Khalid University, Guraiger, Abha, Kingdom of Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rajasekhar Chinta,
Department of Pharmacology, Melaka Manipal Medical College, Manipal University, Manipal-576104, Karnataka, India.
E-mail: naaneeraj99@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 07, 2016**
Date of Peer Review: **Oct 07, 2016**
Date of Acceptance: **Feb 20, 2017**
Date of Publishing: **May 01, 2017**