ORIGINAL ARTICLE

Ameliorative effect of *Cinnamomum zeylanicum* extracts on adiposity, insulin sensitivity and cardiometabolic risk factors associated with insulin resistance in high fructose-fed rats.

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Abstract

Introduction: Evidence(s) established that high fructose (HFr) diet may be responsible for the development of insulin resistance (IR). The aim is to appraise the ameliorative effects of *Cinnamomum zeylanicum* bark extracts on adiposity, insulin sensitivity (IS) and cardiometabolic markers in HFr diet-induced IR. **Materials and Methods:** A total of 30 Wistar male albino rats (240–300 g) were divided into five groups ($n = 6$) and had free access to both diet and water. Groups I and II served as normal control and HFr control (HFrC), received gum acacia (2%) and fructose (60% w/v) diet. Groups III-V were orally administered pioglitazone (PGZ 50 mg/kg/b.wt), aqueous (Cinnamon bark aqueous extract [CBAE] 1 g/kg/b.wt), and ethanolic (Cinnamon bark ethanolic extract [CBEE] 1 g/kg/b.wt) extracts of cinnamon bark, respectively, from day 28 onwards till end of the study. All the groups, except normal control received HFr diet for 42 days. At the end weight gain, adiposity, adiponectin, and cardiometabolic markers (C-reactive protein and uric acid), and cardiovascular (CV) risks, IR and IS indices were evaluated. **Results:** HFr feeding significantly increased weight gain, adiposity and decreased adiponectin levels along with increased cardiometabolic markers as compared to normal control. HFrC significantly increased the CV and decreased IS indices as compared to normal control. PGZ, CBAE, and CBEE groups significantly reduced adiposity, and both cinnamon groups had decreased the weight gain as compared to HFrC. PGZ and CBAE significantly increased adiponectin levels, whereas cinnamon groups and PGZ had decreased cardiometabolic markers as compared to HFrC. Similarly, PGZ and cinnamon extracts had improved IS as compared to HFrC. **Conclusion:** The study concluded that cinnamon extracts had exhibited insulin-sensitizing effects in IR and associated metabolic risk factors by modulating adiponectin in HFr fed rats. Therefore, the study proposes to use cinnamon as a functional food supplement in the management of diabetes and obesity.

Key words: Adiponectin, adiposity, cardiometabolic risks, cinnamon, fructose, insulin sensitivity

INTRODUCTION

Insulin resistance (IR) is due to either decreased or loss of insulin sensitivity (IS) in the target tissues such as liver, skeletal muscle, and adipose tissues (AT).[1] It is characterized by several interrelated metabolic abnormalities, including dyslipidemia, hyperglycemia, hyperinsulinemia, and hypertension.[2] The incidence and prevalence of IR had increased worldwide and primarily attributable to lifestyle modifications.[3]

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AT widely distributed around subcutaneous, viscera and perivascular tissues. It primarily stores triglycerides (TG) and releases free fatty acid (FFA) and glycerol in response to energy demands and majorly contributes to peripheral IR.[4] Dysfunctional AT plays a key role in the etiology and pathogenesis of obesity-related IR. Increased adiposity with AT enlargement and infiltration of macrophage enhances the release of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF-α) and interleukins (IL-6), monocyte chemoattractant protein 1 and resist in to contribute inflammation. In contrast, a decrease in the release of adiponectin and downregulation of peroxisome proliferator-activated receptor γ (PPARγ) in adipocytes results in the impairment of insulin signaling and promotes IR. Adiponectin exerts insulin-sensitizing, anti-inflammatory actions and also regulates adiposity.[2,5,6] Adipocytokines derived from AT, determines IS and glucose homeostasis, provide a molecular connection with increased adiposity and impaired IS.[7] Moreover, IR often recognized as a chronic inflammatory condition. C-reactive protein (CRP) is a sensitive marker for low-grade inflammation, associated with IR and also serves as a clinical tool for cardiometabolic risk assessment.[8] Hence, these are promising molecular targets for the development of insulin sensitizers and or identification of dietary supplements for IR.

Consumption of sugar-sweetened beverages or high fructose (HFr) corn syrup has increased in all age groups of between 10 and 50 years and widely linked to cardiovascular (CV) and metabolic diseases.[9] Clinical studies have shown that fructose intake (100 mg/day) as a sweetener, derives excess calories which promotes weight gain. The liquid fructose is more dangerous than a solid diet and the excess energy generated would be responsible for the decrease in food intake. Evidence suggested that the HFr diet had reduced IS and increased cardiometabolic risks, due to increased hepatic *de novo* lipogenesis, central adiposity along with increased uric acid levels were observed in both humans and rodents.[10,11] Hence, this animal model would be useful to understand the molecular mechanisms underlying the IR induced by HFr diet.

Pioglitazone (PGZ) is a thiazolidinedione, most commonly used in the treatment of IR associated type 2 diabetes. It enhances the transcriptional activation of PPAR-γ to mediate antihyperglycemic, antihyperlipidemic, anti-inflammatory, and antioxidant activities. The unwanted effects of PGZ include weight gain, hip fractures, heart failure, bladder cancer, and non-recommendable for obese and CV diseases (CVD) patients.[12,13]

Till date, there is no safer insulin sensitizers available and often individuals with IR use either medicinal plants or alternative therapies and their efficacy is still undetermined.[14] Since ages, the importance of several medicinal plants has been mentioned in the treatment of diabetes. One such plant is *Cinnamomum zeylanicum* (family-Lauraceae), has shown numerous pharmacological properties, such as anti-inflammatory,[15] antiarthritic,[16] antimicrobial,[17] and antioxidant[18] activities. *In vitro* and *in vivo* antidiabetic studies on *C. zeylanicum* bark have shown to promote insulin receptor phosphorylation, insulin signaling, and enhancing IS.[19-21] Similarly, cinnamon has exhibited hypolipidemic effects in both diabetic and hyperlipidemic models.[22,23] However, there is a relative lack of scientific data regarding the beneficial effects of *C. zeylanicum* as compared to PGZ in IR associated metabolic abnormalities. This study is to investigate the insulin-sensitizing effects of cinnamon bark extracts in the HFr diet-induced IR model. Thus, we hypothesized that cinnamon supplementation has a modulatory role in mitigating adiponectin, cardiometabolic and inflammation associated with IR.

MATERIALS AND METHODS

Animals

All procedures were conducted as per the Committee for the Purpose of Control and Supervision of Experiments on Animals guidelines, and the experimental protocol was approved by the Institutional Animal Committee (IAEC) of the K.S. Hegde Medical Academy, Mangalore (Ref. KSHEMA/IAEC/16/2015). Male albino rats, weighing 240–300 g was housed under controlled conditions of temperature (22 ± 3°C) and humidity (55 ± 5%) with a 12-h light/dark cycle. Throughout the period, all the animals had free access to standard food and water *ad libitum*.

Plant Extracts

Aqueous and ethanolic extracts of *C. zeylanicum* bark (batch. no CIN/D26/STD01 and STD02) were received from Green Chem, Bengaluru.

Chemicals and Reagent Kits

Fructose (LOBA Chemie Pvt. Ltd.), PGZ (Piomed Tablets, Ipca Laboratories Pvt. Ltd.), and ketamine (Aneket vial, Neon Laboratories Ltd. Mumbai) were obtained from the respective sources. All the other chemicals and reagents used in this study were of analytical grade. Both the uric acid and CRP kits (Agappe Diagnostics, Kerala) and adiponectin kit (RayBio, Delhi) were procured from the mentioned suppliers.

Experimental Protocol

After 1-week of acclimatization period, all the rats were randomly assigned to the following five groups of six in each ($n = 6$).

Group I: Normal control received 2% gum acacia and
Group II: HFr control (HFrC) received fructose (60% w/v) dissolved in their drinking water for 42 days to induce IR.
Group III: PGZ 50 mg/kg/b.wt, p.o was administered to HFr fed rats.

Group IV: Cinnamon bark aqueous extract (CBAE) (1 g/kg/b.wt, p.o) was administered to HFr fed rats.

Group V: Cinnamon bark ethanolic extract (CBEE) (1 g/kg/b.wt,p.o) was administered to HFr fed rats.

During the study, HFr diet was given to all the groups (except normal control) for 42 days. The freshly prepared PGZ and cinnamon extracts (suspended in 2% gum acacia) were administered per orally, from day 28 onward along with HFr diet till the end of the experimental period.[24] Body weights were recorded, and on day 42, blood samples were collected by a retro-orbital puncture from overnight fasted rats under ketamine anesthesia. Immediately samples were centrifuged (3000RPM for 10 min) and stored at −20°C until analysis. After the animal sacrification, individual epididymal, perirenal, and retroperitoneal fat pad mass were isolated and weighed.

Biochemical Investigations

Serum uric acid and CRP levels were analyzed through semi-auto analyzer and adiponectin through Enzyme-Linked Immunosorbent Assay. All these investigations were carried in the Central research laboratory, K.S. Hegde Medical Academy.

Assessment of Weight Gain, Adiposity, and Adiposity Index (ADI)

Weight gain was calculated by subtracting initial from final body weights of all the animals.

Visceral adiposity is the sum of white AT (WATs) such as epididymal, perirenal, and retroperitoneal fat of all the rats.

ADI is a ratio of visceral fat weight to body weight and expressed as adiposity percentage (%).[25]

$$ADI - \frac{\text{Sum of total fat pad mass}}{\text{Body weight}} \times 100$$

Assessment of CV Risks and Percentage of Protection

Atherogenic index (AI), coronary risk index (CRI), CV risk index (CVRI), and TG/HDL ratio and anti-AI (AAI), and the percentage of protection (%) were determined to predict atherosclerosis and CV risks by the following equations: [26-30]

$$\text{AI} = \text{TC} - \frac{\text{HDL}}{\text{HDL}}$$

$$\text{CRI} = \frac{\text{TC}}{\text{HDL}}$$

$$\text{CVRI} = \frac{\text{LDL}}{\text{HDL}}$$

$$\text{TG} - \text{HDL ratio} = \frac{\text{TG}}{\text{HDL}}$$

$$\text{AAI} = \frac{\text{HDL}}{\text{TC} - \text{HDL}} \times 100$$

$$\text{Percentage of protection} = \frac{\text{AI of HFr} - \text{AI of test groups}}{\text{AI of HFr control}} \times 100$$

Assessment of IS

Homeostasis Model Assessment-Adiponectin (HOMA-AD) is a novel, modified, and most accurate index for determining IR by using adiponectin.[31] Quantitative IS check index (QUICKI) and TG and glucose (TyG) were used to assess IS.[31,32]

$$\text{HOMA} - \text{AD} = \frac{[\text{Insulin } (\mu\text{IU/mL} \times \text{Glucose } (\text{mg/dl})]}{[405 \times \text{Adiponectin } (\text{mg/ml})]}$$

$$\text{QUICKI} = \frac{1}{[\log \text{Insulin } (\mu\text{U/ml}) + \log \text{Glucose } (\text{mg/dl})]}$$

$$\text{TyG} = \frac{\text{Ln}[\text{Triglycerides } (\text{mg/dl}) \times \text{Glucose } (\text{mg/dl})]}{2}$$

Statistical Analysis

All parameters are expressed as mean ± Standard error of the mean. Statistical analysis was performed using one-way analysis of variance followed by Tukey's test in GraphPad prism 5.0 and $P < 0.05$ set as the level of significance.

RESULTS

Effect of *C. zeylanicum* Extracts on Weight Gain and Adiposity and ADI in HFr Fed Rats

HFr diet feeding for 6 weeks, significantly ($P < 0.001$) increased weight gain, individual WAT (such as epididymal, perirenal, and retroperitoneal) and ADI, respectively, indicates the development of obesity and visceral adiposity, compared to normal control. Administration of CBAE and CBEE, significantly ($P < 0.001$ and $P < 0.01$) reverse the increased weight gain and ($P < 0.01$ and $P < 0.05$) epididymal, ($P < 0.001$ and $P < 0.01$) perirenal + retroperitoneal, and ($P < 0.001$) adiposity and ADI as comparatively to HFrC. Conversely, PGZ facilitated the weight gain and significantly ($P < 0.001$) decreased WATs, adiposity, and ADI, compared to HFrC [Figure 1].

Effect of *C. zeylanicum* Extracts on Adiponectin Levels in HFr Fed Rats

HFr diet significantly (P< 0.001) induced hypoadiponectinemia as evidenced by a decrease in adiponectin levels, as compared to normal control. However, administration of PGZ and CBAE, significantly (P<0.001) reverse the decreased adiponectin levels as compared to HFrC [Table 1]. Similarly to PGZ, CBAE has shown modulatory effects on adiponectin and may be involved in decreases of weight gain, and visceral adiposity in HFr fed rats.

Effect of *C. zeylanicum* extracts on the Inflammatory Marker and Cardiometabolic Risk Factors in HFr Fed Rats

In comparison to normal control, HFr feeding significantly (P < 0.001) increased CRP and uric acid levels, indicates the development of inflammation as well as increased cardiometabolic risks. PGZ had shown a significant (P < 0.01) reversal effect on CRP and (P < 0.001) uric acid levels as compared to HFrC. Similarly, CBEE had significantly (P < 0.01) decreased CRP levels and both cinnamon groups significantly (P < 0.001 and P < 0.01) reduced uric acid levels, as compared to HFrC [Table 1].

Effect of *C. zeylanicum* Extracts on CV Risk Indices in HFr Fed Rats

At the end of the study, HFrC significantly (P < 0.001) increased AI, CRI, CVRI, and TG/HDL ratio and (P < 0.001) decreased AAI as compared to normal control. Oral administration of PGZ, CBAE, and CBEE significantly reversed the increased (P < 0.001) AI, (P < 0.001) CRI, (P < 0.001) CVRI, and (P < 0.001) TG/HDL ratio in comparison to HFrC. Moreover, PGZ and CBAE significantly (P < 0.01 and P < 0.05) improved the AAI in comparison to HFrC. Similar to PGZ, both cinnamon groups offer a significant (80.72,

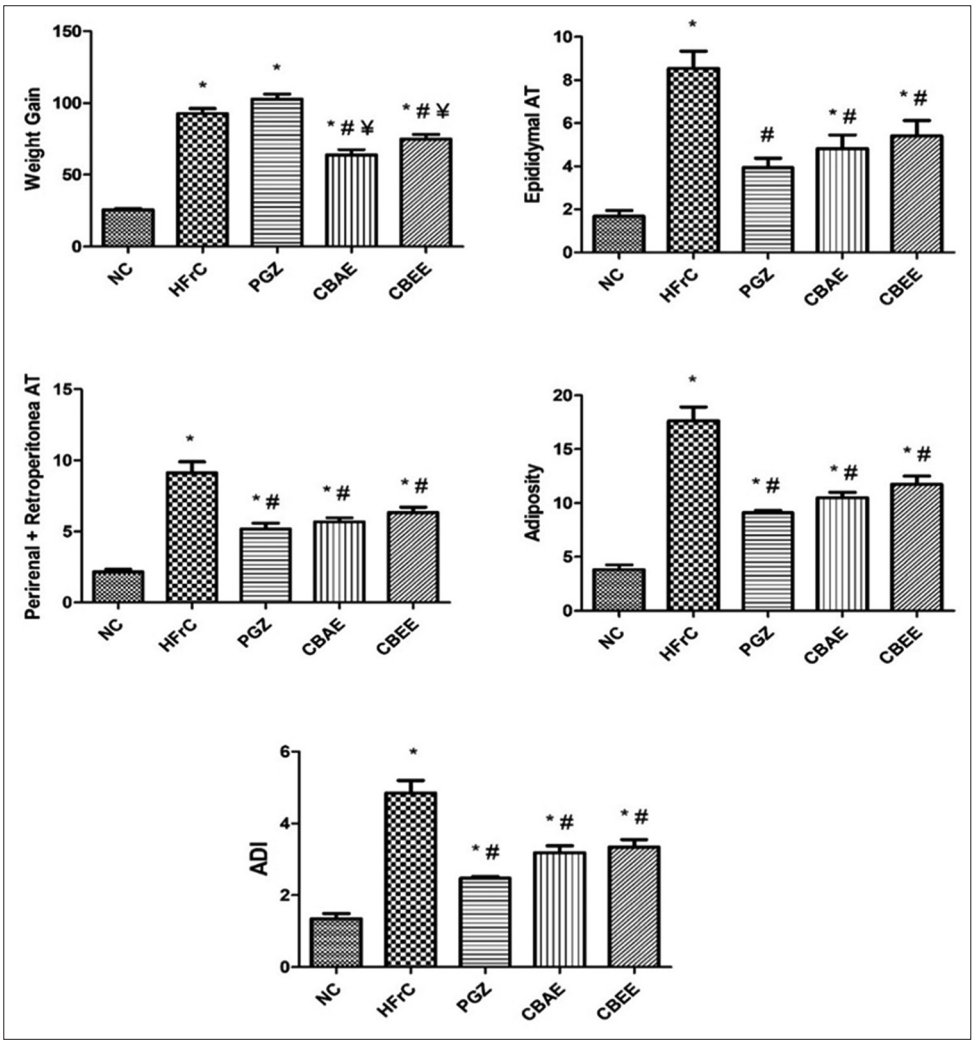

Figure 1: Effect of *Cinnamomum zeylanicum* Extracts on weight gain, adiposity, and adiposity index in HFr fed rats. Values are expressed as mean ± SEM (n = 6) *# and¥ as compared to NC, HFrC, and PGZ groups, respectively, SEM: Standard error of mean, NC: Normal control, HFrC: High Fructose control, PGZ: Pioglitazone, CBAE: Cinnamon bark aqueous extract, and CBEE: Cinnamon bark ethanolic extract, AT: Adipose tissue, and ADI: Adiposity index

Table 1: Effect of *C. zeylanicum* extracts on adiponectin, CRP and Uric acid in HFr fed rats

Groups	Group names	Adiponectin (ng/ml)	CRP (mg/l)	Uric acid (mg/dl)
I	Normal control	82.19±8.76	0.25±0.09	2.11±0.33
II	HFrC	19.14±3.24*	3.42±0.57*	7.34±0.88*
III	PGZ	65.23±5.05#	1.16±0.20#	3.82±0.25#
IV	CBAE	57.62±6.50*#	2.53±0.43*	3.24±0.2#
V	CBEE	36.87±3.99*¥	1.35±0.49#	4.32±0.66#

Data are represented as Mean±SEM (n=6). *, # and ¥ represents as compared to NC, HFrC, and PGZ groups on day-42. SEM: Standard error of the mean, CRP: C- reactive protein, NC: Normal control, HFrC: High Fructose control, PGZ: Pioglitazone, CBAE: Cinnamon bark aqueous extract, and CBEE: Cinnamon bark ethanolic extract. *C. zeylanicum: Cinnamomum zeylanicum*

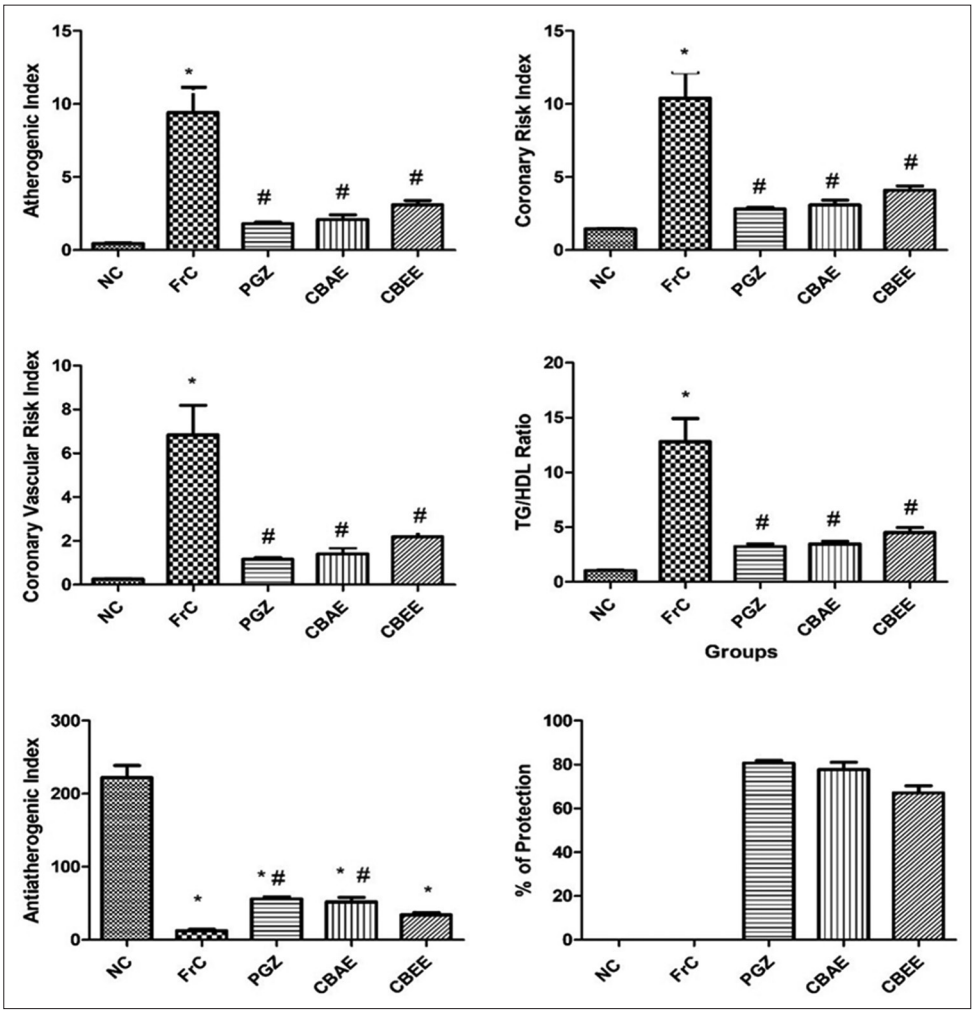

Figure 2: Effect of *Cinnamomum zeylanicum* extracts on cardiovascular risk indices in HFr fed rats. Data are represents as mean ± SEM (n = 6) *# and ¥ as compared to NC, HFrC, and PGZ respectively. SEM: Standard error of the mean, NC: Normal control, HFrC: High Fructose control, PGZ: Pioglitazone, CBAE: Cinnamon bark aqueous extract, CBEE: Cinnamon bark ethanolic extract, TG: Triglyceride and HDL: High density lipoprotein

77.72, and 67.12%) protection against the development of atherosclerotic CVD in HFr fed rats [Figure 2].

Effect of *C. zeylanicum* Extracts on IS in HFr Fed Rats

The results depict that, a significant ($P < 0.001$) increase in HOMA-AD and ($P < 0.001$) TyG and a significant ($P < 0.001$) decrease in QUICKI index values indicate a decrease in IS, confirms the establishment of IR in HFr fed rats, as compared to normal control [Table 2]. At the end of the intervention, PGZ had significantly ($P < 0.001$) reversed the increased HOMA-AD, TyG and improved QUICKI index values, as comparatively to HFrC. CBAE and CBEE groups significantly ($P < 0.001$) reverse the increased both HOMA-AD, TyG, and CBAE had alone shown significant ($P < 0.05$) improvement

Table 2: Effect of *C. zeylanicum* extracts on IS in HFr fed rats

Groups	Group names	HOMA-AD	TyG	QUICKI
I	Normal control	1056.24±198.5	8.06±0.09	0.287±0.007
II	HFrC	3927.28±6588*	10.08±0.06*	0.226±0.002*
III	PGZ	3207.83±377.9#	9±0.04*#	0.256±0.004*#
IV	CBAE	5724.87±836.7#	9.26±0.04*#¥	0.245±0.002*#
V	CBEE	11220.13±1369#	9.51±0.05*#¥	0.239±0.004*

Data are represented as Mean±SEM (n=6). *, # and ¥ represents as compared to NC, HFrC, and PGZ groups on day-42. SEM: Standard error of the mean, HOMA-AD: Homeostasis model of assessment adiponectin, TyG: Triglyceride and glucose index, QUICKI: Quantitative insulin sensitivity check index. NC: Normal control, HFrC: High Fructose control, PGZ: Pioglitazone, CBAE: Cinnamon bark aqueous extract and CBEE: Cinnamon bark ethanolic extract. *C. zeylanicum: Cinnamomum zeylanicum*

in QUICKI index values as compared to HFrC. Moreover, cinnamon groups demonstrated significant ($P < 0.001$) difference with TyG and QUICKI index values, as compared to normal control. Similarly to PGZ, cinnamon groups also modulated above surrogate markers of IR and responsible for the improvement of IS.

DISCUSSION

IR predispose and predicts type-2 diabetes, obesity, and CVD.[6] Hence, there is a need for the development of new drug targets to reverse its clinical importance. Similarly to Chen *et al.* and Abdullah *et al.,* the present study also established IR. HFr diet had induced weight gain, visceral adiposity, and hypoadiponectinemia with increased cardio-metabolic adverse effects.[9,33] HFr is a calorie enriched diet, amenable for an imbalance between food intake and energy expenditure that leads to increased weight gain. AT regulates energy homeostasis, carbohydrate as well as lipid metabolism and also IS, while AT dysfunction promotes weight gain, visceral adiposity, and IR.[25,34] Since adiponectin enhances FFA oxidation; therefore, hypoadiponectinemia would also encourage weight gain and visceral adiposity as observed in HFrC.[12] Administration of PGZ had promoted, and cinnamon extracts had reversed the weight gain in HFr fed rats. Moreover, intervention groups have shown to decrease both visceral adiposity and ADI; perhaps due to either decrease in energy storage or an increase in energy expenditure along with restored adiponectin levels.[4] Therefore, cinnamon might balance energy homeostasis, as the relationship exists between WAT and energy storage. Their beneficial effect on weight gain can be attributed to PPAR-α activation while a decrease in visceral adiposity results from the net effect of PPAR−α/+γ receptors.[12]

Adiponectin plays a key role against IR, and hence administration of adiponectin in diabetic mice attenuates glucose excursions and plasma non-esterified fatty acids and thus improves IS.[4-6] In both the human and animal models, decreased expression of adipose adiponectin and adiponectin levels with down-regulation of PPAR γ receptors results in IR.[34] This study also demonstrated HFr induced hypoadiponectinemia that could have majorly contributed to the development of IR in these rats. However, supplementation of PGZ and CBAE had increased adiponectin levels, which had decreased adiposity and additionally ameliorates insulin-stimulated glucose utilization that contributed to insulin-sensitizing effects in IR rats.[12,35]

Inflammation is either due to elevated levels of pro-inflammatory cytokines or CRP and along with decreased adiponectin levels are responsible for IR.[8,13] CRP is an acute phase protein, released under the stimulation of TNF-α and IL-6. Often chronic low-grade inflammation decreases IS and play a pathological role in the development of IR and diabetes.[36] HFr feeding significantly increased the CRP levels along with hypoadiponectinemia, lead to induce chronic inflammation. The results exhibited that PGZ and CBEE groups had reduced CRP levels and whereas, PGZ and CBAE reversed hypoadiponectinemia in IR rats. It indicates that PGZ and cinnamon groups had modulated the CRP and adiponectin to increase the transcription of PPAR-γ genes to exert their anti-inflammatory effects and also involved in the decrease of IR.[2,5]

Increased CV risk indices and conversely decreased the percentage of protection and AAI, denotes the development of CVD in HFrC. Simultaneously, HFrC exhibited persistent hyperlipidemia and hyperglycemia that was observed in our previous study, also related to the CVD in IR rats. Moreover, CRP is an independent marker of CVD, triggers very-low-density lipoprotein and remnant lipoprotein to activate platelet aggregation, was significantly elevated in HFrC.[37] In this study, HFr diet disrupted the fat consumption and oxidation that leads to hyperlipidemia and along with hypoadiponectinemia, contributed to increase atherosclerosis and plaque formation.[38] Furthermore, increased visceral adiposity itself increases cardiometabolic risk. All the intervention groups had decreased CV risk indices, CRP and also increased the percentage of protection and AAI index. Hypolipidemic effects of PGZ and cinnamon, partly attributed to elevated adiponectin levels which activates PPAR-γ receptors in WAT and or inhibiting lipid synthesis or decreases lipoprotein levels depicts their cardioprotective effects.[25] Their antiatherogenic effects can be clarified by the activation of lipoprotein lipase and lecithin cholesterol acyltransferase to reverse hypertriglyceridemia and to increase HDL levels.[12] In acquiescing to Ibrahim *et al.* and Vazquez Prieto *et al.* that

hyperuricemia in HFr fed rats enhances the release of oxidized lipids and inflammatory markers that promote oxidative stress and vascular inflammation.[12,39] Moreover, hyperuricemia also inhibits endothelial nitric oxide generation and produces renal vasoconstriction that contributes to hypertension and cardiometabolic diseases. Therefore, hyperuricemia can predict the development of obesity, hypertension, IR, and diabetes.[40] Both PGZ and cinnamon have a beneficial effect against cardiometabolic risk and oxidative stress accompanied in IR.

IS at both peripheral and hepatic tissues is declined in IR. Several studies had demonstrated that HFr diet-induced hyperglycemia, hyperlipidemia, impaired glucose tolerance, and adiposity, and altogether diminishes IS.[41,42] Hypertriglyceridemia and FFA level decreases IS, as they can interfere with insulin signaling and or action, and the former is an essential marker of IR.[5] HFr diet significantly increases IR indices (HOMA-AD and TyG) with a concomitant decrease of IS index (QUICKI), propose the development of IR. Both the PGZ and cinnamon extracts had significantly reversed the increased IR indices and improved IS index in IR rats. Reversal effects of PGZ and cinnamon extracts against HFr induced IR can be attributed through its ability to reduce fasting glucose, insulin, and HOMA-IR that was observed in our earlier work. Furthermore, PGZ and CBAE had also increased adiponectin levels were in agreement with IS index and speculated to improve IS in IR rats.[43]

CONCLUSION

The study concluded that cinnamon effectively restored IS and could be used as a dietary regimen in the management of IR associated metabolic abnormalities. Therefore, cinnamon is hypothesized to activate various PPARs mediated pathways in regulating metabolic homeostasis, AT differentiation and adiponectin release to ameliorate IS. However, for a better empathizing of the molecular mechanism of cinnamon, expression of various adipocytokines, AT signaling, and PPAR receptors in HFr fed rats are required in further research.

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