

Cardioprotective effect of *Cinnamomum zeylanicum* extract on rats fed on high fat high fructose diet

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Abstract

Background: As a result of the increased consumption of sugar-rich and fatty-products, and the increase in the preference for such products, metabolic disorders are becoming more common at a younger age. Hyperlipidemia, insulin resistance [IR] and inflammatory status induced by high fat high fructose diet [HFHFD] increase the risk of developing cardiovascular diseases [CVDs] which are the leading cause of death worldwide. **Objective:** This study is aiming to determine the effects of HFHFD on cardiovascular disease [CVD]-related parameters. Also, the possible protective and curative effects of cinnamon extract on cardiac diseases. **Methodology:** Fifty adult male Sprague Dawley rats were divided into five groups: Group I: [control]. Group II rats were fed a diet with 45 kcal% fat and drink fructose 60% [HFHFD] for 8w. Group III: fed on HFHFD and pioglitazone [PGZ 20 mg/kg/b.wt]. Group IV: fed on HFHFD and cinnamon extract 200mg/kg.b.w. Group V: fed on HFHFD and treated with combination of PGZ drug and cinnamon extract. At the end of the experiment, blood glucose, serum insulin, lipid profile, and oxidative stress markers were done. Heart tissues were used for Inflammatory cytokines [tumor necrosis factor- α [TNF- α] and interleukin 6 [IL-6], nuclear factor kappa [NF- κ B], and cardiac enzymes beside histopathological examination. **Results:** HFHFD administration resulted signs of cardiomyopathy revealed by significant increase in blood glucose, serum insulin, homeostasis model assessment of IR [HOMA- IR] index with disturbed lipid profile. Also, significant increase in serum cardiac enzymes, inflammatory cytokines and oxidative stress markers were also noticed. PGZ and cinnamon extract treatment resulted in a significant decrease in glucose, insulin, and HOMA- IR index, amelioration of lipid profile, cardiac enzymes, inflammatory cytokines and oxidative stress markers. **Conclusion:** The current study revealed that cinnamon extract improves cardiomyopathy resulted from HFHFD administration possibly via hypolipidemic, anti-inflammatory and anti-oxidative ways. It can be used as food supplement has cardioprotective role in patients with metabolic disorders

INTRODUCTION

Food and beverages rich in energy, fat, and/or sugar are now commonly consumed in modern societies [1]. Consumption of sugar-sweetened beverages or high fructose corn syrup has increased in all age groups between 10 and 50 years and widely linked to cardiovascular and metabolic diseases [2]. Fructose is used commercially as a sweetening substitute [fructose corn syrup] for glucose or sucrose, in the preparation of desserts, condiments, and carbonated beverages. It has been confirmed that consumption of high amounts of refined carbohydrates in food and beverage increases the risk of dyslipidaemia [3], obesity, insulin resistance and heart disease [4].

Evidence suggested that the high fructose diet had reduced insulin sensitivity 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 [5].

In addition, a high fructose diet is known to lead hypertension and insulin resistance in animals [6]. Insulin resistance has been proposed as an underlying mechanism that links endothelial dysfunction factors such as endothelial nitric oxide synthase [eNOS] and Endothelin-1 [ET-1] [7]. Also, chronic exposure of dyslipidemia has a major effect on cardiovascular disease [CVD] [8].

Obesity is characterized not only by exacerbated inflammatory outcomes, but also by

Permanent increased oxidative stress [9]. This imbalance between antioxidant and pro-oxidant factors is strongly related to pro-inflammatory processes [10], leading to the development of obesity-related complications, atherosclerosis, and CVD [11]. Mitochondria are the primary source of reactive oxygen species [ROS]. Their production

and oxidative damage may contribute to the onset and progression of CVD, obesity, diabetes, and atherosclerosis [12].

The synthesis of ROS promoted an inflammatory status and dysregulated the expression of inflammation-associated adipocytokines in metabolic syndrome, contributing to obesity-related cardiovascular risk through endothelial dysfunction and platelet activation [13].

Although there is different data regarding the metabolic alterations in obese rats and the development of cardiac changes, no clear evidence concerning obesity-related oxidative stress and inflammation in the heart is present. Thus, investigating the interplay between these risk factors with obesity/metabolic syndrome [MetS] onset as well as the interactions with CVD is fundamental [14].

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 CVD patients [15].

Herbals are nowadays used in wide ranges for medical purposes lacking the side effects on the prolonged administrations of synthetic drugs, so we attended to try another natural agent which is cinnamon extract. Cinnamon is the bark of the *Cinnamomum cassia*. It contains cinnamic aldehyde, cinnamic acid, tannin and Methyl-Hydroxychalcone Polymer [MHCP] as main components [16].

Cinnamon Extract [CE] contains biologically active substances with insulin-mimetic properties [16]. Qin et al. [17] have reported that cinnamon extract decreases blood glucose and lipid profiles

in rats and increases insulin sensitivity and glucose uptake in adipocytes [18]. Moreover, it possess the ability to reduce lipid levels in fructose-fed rats and affects immune responses by regulating anti-, proinflammatory and glucose transporter gene expressions in mouse macrophages [19]. It has been shown that, cinnamon extract has antioxidant activity [20]. Therefore, the use of CE as herbal medicine has received attention.

Therefore, this study was designed to evaluate the effect of cinnamon extract [CE] and selective PPAR γ agonist PGZ treatment on cardiac dysfunction induced by high fat high fructose diet.

MATERIAL and METHODS

Experimental design

Fifty adult male Sprague Dawley rats weighing 120 – 150 g were obtained from Nile center for experimental studies and researches [Al-Mansoura, Egypt], housed in wire covered cages in a room maintained at constant room temperature [23 \pm 1 $^{\circ}$ C], humidity [60 \pm 10%], and a 12-/12-h light/dark cycle. Rats acclimatized for one week before the beginning of any experimental procedures and allowed standard rat chow and water ad libitum. They were kept for one week on their normal diet and free access to water for acclimatization before starting the experiment. All procedures were approved by the Animal Care Committee of Al-Azhar University, as well as specific national laws where applicable. The rats were divided into 5 equal groups as follows:

- **Group I [Control]:** rats fed on normal rat chow and received 2% gum acacia.
- **Group II [HFHFD group]:** Rats were fed on western rat diet, had an Atwater fuel energy of 4.6 kcal/g and comprised 50% crude carbohydrate, 21.4% crude fat, 17.5% crude protein, 3.5% crude

fibre, 4.1% ash [21] and received fructose [60% w/v] dissolved in their drinking water for 8 weeks.

- **Group III: [PGZ]:** Rats were fed on HFHFD and administrated with PGZ drug [20 mg/kg] [22] per orally once a day for 4 weeks after induction of Met S.
- **Group IV [cinnamon]:** Rats were fed on normal rat chow and received cinnamon extract 200 mg/kg orally once a day according to Khan et al [23] for 8 weeks.
- **Group V [combination]:** Rats in this group received HFHFD and treated with CE and PGZ. Cinnamon extract [200 mg/kg b.wt] once daily given orally from the 1st day while PGZ [20 mg/kg/b.wt] was administered for 4 weeks after induction of Met S.
- **Drugs and Herb:**
- Fructose [LOBA Chemie Pvt. Ltd.], PGZ [Piomed Tablets, Ipca Laboratories Pvt. Ltd.] Cinnamon was purchased from local market.
- **Cinnamon extract preparation**
- Cinnamon aqueous extract was extracted based on method of sheng et al [24].
- Cinnamon powder 200g was dissolved in 1000 ml double distilled water then subjected for revolving evaporator in vacuum state using vacuum pump till the volume of water reduced to about 50%. The supernatant was filtered using Whatman filter paper to obtain cinnamon extract at pharmacognosy department lab, faculty of pharmacy, Al-Azhar University.

At the end of the experiment, blood was collected from the tail vein. Serum was separated and stored frozen at -20 $^{\circ}$ C until the time of analysis to assess [blood glucose, insulin and homeostasis model assessment of IR [HOMA- IR] index], parameters of lipid profile [TG, TC, HDL, LDL], oxidative stress markers [TAC, GPX, MDA, SOD] inflammatory cytokines [TNF $-\alpha$, IL-6 NF-Kb]

and cardiac functions by estimating: cardiac enzymes lactate dehydrogenase [LDH] and creatine kinase [CK- MB] levels.

Animal chest was opened; the heart was isolated and was longitudinally cut. One half was used for estimation of inflammatory cytokines and the other half was used for histopathological examination.

Blood pressure analysis

Systolic arterial blood pressure was assessed one week before induction and at weeks 6 the diet via a non-invasive tail cuff method [CODA Blood Pressure System, Kent Scientific Corp., Connecticut, USA]

Biochemical measurements:

1. - Estimation of IR: The serum glucose was assayed colorimetrically by the method adopted by **Tietz [25]**. Insulin concentration were measured in serum samples by enzyme immunoassay using the rat insulin ELISA kits [26] and HOMA-IR index was calculated using the equation: [Insulin in $\mu\text{IU/L}$] \times [glucose in mmol/L] divided by 22.5 [27].

2. - Estimation of Lipid profile: TG level was measured in plasma by quantitative- enzymatic - colorimetric procedure according to the method of **França et al. [28]** using a triglycerides colorimetric assay kit from Cayman Chemical Company. TC level was measured in plasma by quantitative - enzymatic - colorimetric procedure according to the method of **MacLachlan et al. [29]** using a cholesterol quantitation kit from Calbiochem Company and HDL-C was measured in plasma by quantitative - enzymatic colorimetric procedure according to the method of **Trinder [30]** using a HDL-C kit from Bio Med diagnostic Company.

3- Estimation of oxidative stress markers

Thiobarbituric acid reactive substances [TBARS] measured as malondialdehyde [MDA], reduced glutathione [GSH], and total antioxidant capacity [TAC] were measured by colorimetric analysis kit [Biomed diagnostic, Egypt] according to manufacturer's instructions.

4- Determination of cardiac inflammatory markers

The activity of the enzyme LDH was estimated by the method of Teitz using agape Diagnostic Kit and CK-MB was measured by immunoenzymatic method **Okinaka et al. [31]**. Inflammatory cytokines TNF- α and IL-6 [R&D Systems Inc., USA; Catalog Nos. RTA00 and R6000B respectively], NF- κB , [MyBioSource, Inc., USA; Catalog Nos. MBS722386] were assessed using ELISA kit according to manufacturer's instructions.

Histopathological examination

Light microscopic examination: At the end of the experiment, animals were subjected to diethyl ether light anesthesia and then were sacrificed. Animal's chest was opened; the heart was isolated and was longitudinally cut. Half of the heart was used for histopathological examination: fixed in 10% neutral buffered formalin, embedded in paraffin. Sections were cut at 5 μm thickness, then stained with hematoxylin and eosin [H and E] staining and examined by light microscope.

Statistical analysis

Data recorded as mean \pm standard deviation [S.D.]. Comparison was done between 2 groups by ANOVA [P<0.05] was considered as significant] followed by Post-hoc Tukey's test for multiple comparisons. Data were expressed using SPSS version 23.

Results

Table [1]: Comparison between studied groups regarding body weight, systolic blood pressure, blood glucose, insulin, and HOMA-IR [Mean±SD]

| Groups Parameters | Group 1 Control | Group 2 HFHFD | Group 3 PGZ | Group 4 Cinnamon | Group 5 PGZ+ Cinnamon |
|--------------------------|--------------------|--------------------------|--------------------------|----------------------------|-----------------------------|
| Body weight | 233.7±9.2 | 413.5±22.92 ^a | 392.7±8.7 ^{ab} | 279.9±16.18 ^{abc} | 277.2±4.49 ^{abc} |
| Systolic blood pressure | 113.4±3.72 | 138.5±2.46 ^a | 136.5±2.55 ^a | 119.2±3.97 ^{abc} | 122.9±5.76 ^{abc} |
| Blood glucose [mg/dL] | 123.7±4.16 | 185.5±8.21 ^a | 145.0±5.87 ^{ab} | 155.5±7.56 ^{abc} | 139.5±7.93 ^{abd} |
| Insulin [μIU/mL] | 8.58±0.28 | 16.04±1.39 ^a | 11.34±0.58 ^{ab} | 10.55±0.97 ^{ab} | 10.27±0.49 ^{ab} |
| HOMA-IR | 2.62±0.14 | 7.34±0.62 ^a | 4.05±0.42 ^{ab} | 4.06±0.3 ^{abc} | 3.54±0.29 ^{acd} |

Table [2]: Comparison between studied groups regarding lipid profile [Mean±SD].

| Groups Parameters | Group 1 Control | Group 2 HFHFD | Group 3 PGZ | Group 4 Cinnamon | Group 5 PGZ+ Cinnamon |
|----------------------|--------------------|-------------------------|--------------------------|--------------------------|-----------------------------|
| TG [mg/dl] | 136.6±4.99 | 263.5±16.9 ^a | 159.3±8.98 ^{ab} | 155.2±4.64 ^{ab} | 141.8±3.94 ^{bcd} |
| TC [mg/dl] | 15.3±2.16 | 35.4±3.34 ^a | 20.6±1.5 ^{ab} | 19.5±1.35 ^{abc} | 21.8±1.47 ^{abd} |
| LDLc [mg/dl] | 27.8±1.62 | 52.6±2.01 ^a | 30.4±9.71 ^b | 31.2±1.23 ^b | 25.2±8.28 ^b |
| HDLc [mg/dl] | 61.2±2.2 | 29.4±4.86 ^a | 46.5±2.42 ^{ab} | 45.9±1.91 ^{ab} | 47.6±3.5 ^{ab} |

Table [3]: Comparison between studied groups regarding cardiac enzymes and oxidative stress [Mean±SD].

| Groups Parameters | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|-----------------------|-----------|--------------------------|---------------------------|--------------------------|----------------------------|
| GPX u/L0 | 42.2±2.21 | 24.8±2.04 ^a | 26.9±1.52 ^a | 27.7±1.16 ^{ab} | 31.0±1.05 ^{abcd} |
| MDA nmol/L | 17.9±0.99 | 29.2±1.87 ^a | 22.3±1.16 ^{ab} | 20.7±0.95 ^{abc} | 18.1±0.74 ^{bcd} |
| TAC[mmol/l] | 0.89±0.13 | 0.46±0.09 ^a | 1.62±0.12 ^{ab} | 1.45±0.13 ^{abc} | 0.87±0.11 ^{bcd} |
| IL-6 | 3.09±0.51 | 5.29±0.81 ^a | 4.45±0.3 ^{ab} | 4.67±0.13 ^{ab} | 3.89±0.12 ^{abd} |
| TNF-α [Pg/ml] | 53.2±3.68 | 76.9±9.34 ^a | 59.1±6.12 ^b | 65.2±9.31 ^{ab} | 56.1±5.41 ^{bd} |
| NF-κB, | 0.84±0.07 | 1.97±0.22 ^a | 1.47±0.17 ^{ab} | 1.42±0.14 ^{ab} | 1.1±0.11 ^{abcd} |
| Serum LDH [mg/ dl] | 116.6±3.6 | 272.7±21.03 ^a | 165.4±4.38 ^{ab} | 160.2±6.2 ^{ab} | 141.4±2.07 ^{abcd} |
| Serum CK- MB [mg/ dl] | 113.4±1.9 | 231.1±7.42 ^a | 154.0±4.83 ^{abs} | 159.7±6.4 ^{ab} | 145.1±4.23 ^{abcd} |

a indicate significance in comparison to group 1
 b indicate significance in comparison to group 2
 c indicate significance in comparison to group 3
 d indicate significance in comparison to group 4

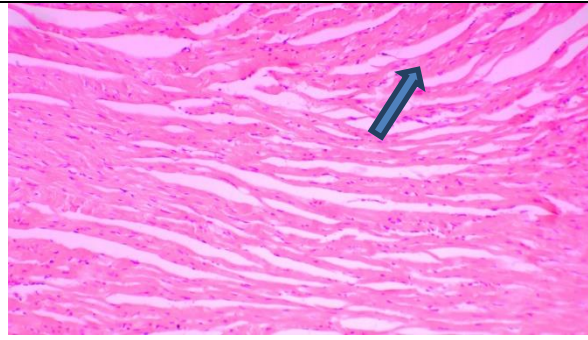


Figure [1]: section of the cardiac muscles shows bundles of muscles with bright eosinophilic cytoplasm interdigitating with each other of the control group [H&E- ×100].

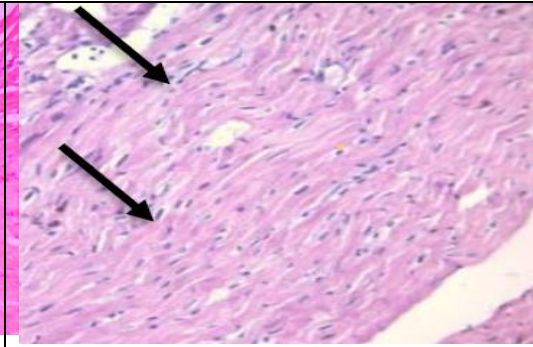


Figure [2]: section of the cardiac muscles shows cellular infiltration, congested blood vessel and widely separated pericardium of the HFHFH group [H&E- ×400].

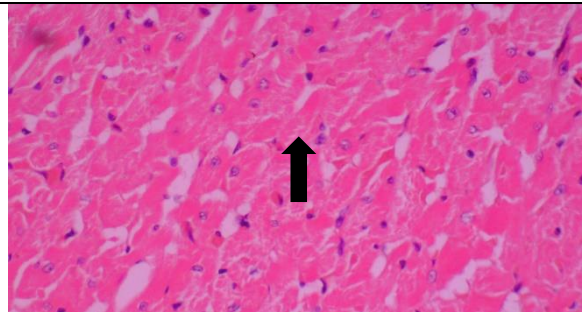


Figure [3]: section of the cardiac muscles shows decrease granularcy of cytoplasm of muscles with partial recovery of degeneration of some of the HFHFH Cinnamon- treated group [H&E- ×400].

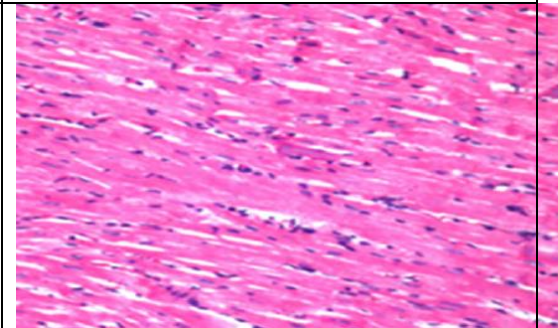


Figure [4]: section of the cardiac muscles shows muscles bundles with bright eosinophilic cytoplasm interdigitating with each other of the HFHFH PGZ - treated group

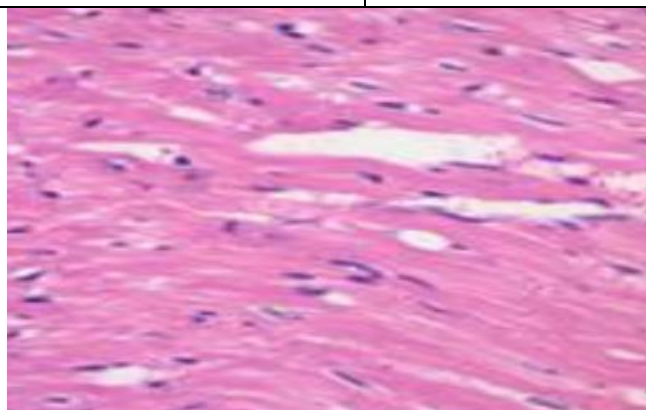


Figure [5]: section of the cardiac muscles shows long, cylindrical muscle fibers with central nucleus showed more improved histological architecture. of the HFHFH combined- treated group

1- Effect of high fat high fructose diet [HFHFD] on Cardiometabolic Risk Factors in rats

Administration of HFHFD for 8 weeks resulted in significant [$P < 0.001$] increase in body weight, compared to normal control. Also, all signs of metabolic syndrome by a significant increase [$P < 0.001$] in systolic blood pressure, blood glucose, serum insulin, HOMA- IR, serum TG, TC, LDLc and significant decrease in serum HDLc [table2]. In addition, cardiac affection was indicated by significant elevation of serum cardiac enzymes [LDH and CK- MB] levels [table3]. Oxidative stress was shown by significant decrease of serum antioxidant enzymes GPX and TAC as well as an increase of MDA. It was noticed an increase of myocardial inflammatory markers [NF- κ B, IL-6, and TNF- α] levels in comparison to normal control, indicating development of inflammation as well increased cardiometabolic risks.

2- Effect of PGZ and cinnamon extract administration to HFHFD fed rats

Treatment with PGZ to rats fed on HFHFD for 8 weeks, resulted in significant [$P < 0.05$] decrease in body weight and improvement of metabolic syndrome [manifested by significant decrease of blood glucose, serum insulin, HOMA- IR, TG, TC and LDLc] and a significant increase in serum HDLc. In addition, it improved the oxidative stress shown by significant elevation of antioxidant enzyme TAC as well as decrease of MDA levels. Improvement of cardiac dysfunction was shown by significant lowering of serum cardiac enzymes LDH and CK- MB levels as well as myocardial levels of TNF- α , NF- κ B, and IL-6. However, no changes were noticed in systolic blood pressure and GPX in comparison to group 2 [table 1,2,3]. LDLc

and TNF- α were Improved to the point of being insignificant with their levels in the control group.

Meanwhile, administration of cinnamon extract for 8 weeks , significantly [$P < 0.001$] reverse the increased weight gain and improved MS manifested by significant [$P < 0.001$] decrease of blood glucose, serum insulin, HOMA- IR. It was noticed that cinnamon supplementation succeeded to improve lipid profile [$P < 0.001$] [decrease TG, TC, and LDLc and significant increase in HDL] with no significance between both groups. Also, cinnamon extract induced a powerful antioxidant effect through elevation of TAC and the reduction of MDA in serum. There were insignificant changes in their levels and those in normal group. Similar to PGZ, improvement of cardiac dysfunction proved by significant lowering of serum cardiac enzymes LDH and CK- MB levels, [$P < 0.01$] decreased myocardial inflammatory cytokines levels [$P < 0.01$] compared to HFHFD fed rats

Combination of both PGZ and cinnamon extract led to more improvement in manifestations of metabolic syndrome more than noticed in treatment with PGZ or cinnamon groups. There was a marked decrease of myocardial proinflammatory cytokines as well as cardiac enzymes significantly in comparison to other groups.

DISCUSSION

In this study, we chose a high fat diet combination with 10% fructose in drinking water to mimic a typical unhealthy Western diet containing high-fat products associated with high-sugar drinks to determine the effects of this diet on CVD related parameters in rats.

The present study revealed that consumption of HFHFD in growing rats significantly increased body weight associated with dyslipidaemia,

hyperinsulinaemia associated with IR compared with other groups. Moreover, excessive oxidative stress [increased MDA and decreased GSH and TAC], with subsequent myocardial inflammation [increased NF- κ B, IL-6, and TNF- α].

Oxidative stress and inflammation are masterful players in the pathogenesis of DCM [32]. In fact, inflammation and oxidative stress are inextricably linked, as they trigger and amplify each other in a vicious cycle [33]. In DCM, ROS production can be redundant by metabolic abnormalities like hyperglycemia and hyperlipidemia leading to oxidative tissue injury and ultimately result in ventricular dysfunction [34]. Additionally, ROS facilitates the activation of the transcription factor NF- κ B, one of the central players in inflammatory signaling that mediates pro-inflammatory gene expression and inflammatory cytokines release, and induces inflammatory myocardial injury [35]. Moreover, NF- κ B-promoted inflammation activates NF- κ B itself [36]

The main pathophysiological mechanism that contributes to the development of cardiomyopathy, cardiac hyper-trophy and insulin-resistant heart is the cardiac dysmetabolism, as reported in the previous study [37]. This metabolic inflexibility caused by internalization of glucose transporter 4 [GLUT4] to its intracellular location and CD36 [mediated uptake of FAs] becomes specially localized to the sarcolemma leaving the fatty acid as the sole fuel source. This shift induces an intramyocardial lipid accumulation due to the increased uptake and accumulation of lipid in the heart [38] which is correlated exactly with histopathological findings in the current study that revealed myocytes hypertrophy and many fat droplets appearance that can induce contractile dysfunction.

All biochemical results and cardiac imaging results agree with observed histopathological changes of the cardiac tissue. H and E staining revealed many fat cells appeared as empty cells with peripherally flattened nuclei, highly congested blood vessels with cellular infiltrations and widely separated pericardium.

Treatment with PGZ for 6 weeks resulted in improvement of Met S manifestations proved by significant decrease in IR parameters and restoration of lipid profile parameters. This manifested improvement mostly refers to ability of PGZ to improve IR and enhance insulin activity. This ability could directly balance the disturbed carbohydrate and lipid metabolism and alleviates the abnormal lipid accumulation that complicates IR [39].

All these biochemical improvements were associated with improvement of histopathological findings with H and E staining including decreased appearance of fat cells, decreased cellular infiltrations and congestion of blood vessels compared to HFHFD group.

Several studies have shown that PGZ irrespective to its blood glucose lowering effect improved different cardiovascular disorders via modulation of myocardial lipid profile, suppression of endoplasmic reticulum stress, inhibition of inflammation, and reduction of ROS [40]. PGZ is also documented to inhibit oxidative stress and ROS production through PPAR- γ -mediated mechanisms [41].

It was established that NF- κ B is a potential downstream target for PPAR- γ [42], where activation of PPAR- γ by PGZ leads to the inhibition of inflammatory responses through preventing the activation of NF- κ B [43]. PGZ is also documented

to inhibit oxidative stress and ROS production through PPAR- γ -mediated mechanisms [40].

Our results agree with other reports which showed that PGZ reduced oxidative stress and endoplasmic reticulum stress [40], prevented Ca^{2+} efflux from the endoplasmic reticulum via increasing SERCA2b expression [44], shortened action potential duration in ventricular myocytes via inhibition of L-type Ca^{2+} current, and produced negative inotropic effects in ventricular myocytes from type 2 diabetic rat via reduction in Ca^{2+} transient [45].

Cinnamon has anti-oxidant activity and also a very strong free radical scavenging activity and have been shown for many extract such as alcoholic, aqueous and etheric of many parts of plant. Phenolic compounds are found in almost all parts of the plants that responsive for anti-oxidant activity of cinnamon and a potent scavenger of hydrogen peroxide, nitric oxide, and lipid peroxide free radicals [46].

One of the most important causes of CVD is obesity. Obesity is a source of proinflammatory cytokines and increase in oxidative stress condition Cinnamaldehyde as an agonist of TRPA1 in epithelial mouse stomach cells reduced cumulative food intake and gastric emptying rates [47].

Cholesterol- and lipid-lowering effects of cinnamon were shown in many studies [48]. In Khan *et al* study, cinnamon with doses of 1, 3, and 6 g per day caused a reduction TG, total cholesterol, and LDL-c cholesterol levels in humans [23].

Inhibiting hepatic HMG Co-A reductase enzyme is the main mechanism for reduction of blood lipid by cinnamon. Reduction in oxidative stress by cinnamon through inhibition of 5-lipoxygenase enzyme is another mechanism that reduces lipid peroxidation. Cinnamon extracts have lipolytic activity. The enhancement of hepatic antioxidant

enzyme activity is a critical role in hypolipidemic characteristics of cinnamon [49].

These biochemical results in the present study are associated with improvement of the histopathological findings with H and E which revealed reduced cellular infiltrations and congestion of blood vessels and less appearance of fat cells.

Alvarez-Collazo *et al.* [50] reported that short term use of cinnamon can significantly reduce blood pressure especially among those who are prediabetic or type 2 diabetic. The activation of the chemosensory cation channel [TRPA1] and L-type currents were more potent in ventricular cardiomyocytes [VCM] than in vascular smooth muscle cells [VSMC]. This effect may contribute to its vasorelaxing action [51]. There is a close association between glycemic indicators [fasting plasma glucose or HbA1c] and systolic and diastolic blood pressure levels [52].

The CVS protective effects of cinnamon were shown in a study by Badalzadeh *et al.* [53]. They stated that the antiathrosclerotic effects and preventive vascular diseases of cinnamon resulted from inhibition of vascular smooth muscle cell proliferation through blockade of thromboxane A2 receptors mediated proliferation by cinnamon.

Khaki [54] reported that use of 75 mg/kg of *C. zeylanicum* for 4 weeks in rats, as an anti-oxidant in food increased SOD, GPX, and CAT that leads to the elimination of ROS as well as decreasing lipoperoxidation [LPO] level and the apoptotic index. In addition cinnamon has anti-LPO in vegetable oil that inhibited MDA, as a marker of LPO production.

Wang *et al.* revealed that antioxidant activity of cinnamaldehyde and its protective effect on endothelial dysfunction in high glucose conditions

is mediated through activating NF-E2-related factor

2 [Nrf2] and up-regulation of the downstream target proteins [55].

Author declares that, the research completely financed by the author himself.

Interestingly, combination regimen including cinnamon extract as well as PGZ revealed more significant anti-fibrotic activity compared with either single treatment protocol. The role of PGZ as PPAR- γ agonist relies on modulation of myocardial pro-inflammatory markers [43; 56] through PPAR- γ dependent and independent effects.

The remarkable effect that was seen with PGZ and cinnamon extract combination regimen may be related to the ability of cinnamon to increase PPAR- γ expression thus augmenting and facilitating the aforementioned cardioprotective effects of PGZ. Our data indicate that PGZ and cinnamon combination regimen has an indisputable effect on inhibiting cardiac dysfunction.

CONCLUSION

These results of the present study showed ameliorative effect of both PGZ and cinnamon extract treatment against all the drastic consequences of cardiomyopathy indicating its protective role against cardiac dysfunction induced by HFHFD. These results may be attributed to by strong hypolipidemic, antioxidant and anti-inflammatory effect that well augmented by PGZ therapy. It has been concluded that cinnamon has potential therapeutic use in metabolic syndrome and can prevent morbidity and mortality due to cardiovascular diseases as a herb with less side effects. Further studies are needed to clarify more values and specific ingredients of cinnamon to answer many of open issues about its biological effects.

Conflicts of interest

Author declares no conflict of interest.

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