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# Therapeutic effects of tender coconut water on oxidative stress in fructose fed insulin resistant hypertensive rats

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ABSTRACT

**Objective:** To investigate whether tender coconut water (TCW) mitigates oxidative stress in fructose fed hypertensive rats. **Methods:** Male Sprague Dawley rats were fed with fructose rich diet and treated with TCW (4 mL/100 g of body weight) for 3 subsequent weeks. Systolic blood pressure was measured every three days using the indirect tail cuff method. At the end of the experimental period, plasma glucose and insulin, serum triglycerides and free fatty acids, lipid peroxidation markers (MDA, hydroperoxides and conjugated dienes) and the activities of antioxidant enzymes were analyzed in all the groups. **Results:** Treatment with TCW significantly lowered the systolic blood pressure and reduced serum triglycerides and free fatty acids. Plasma glucose and insulin levels and lipid peroxidation markers such as MDA, hydroperoxides and conjugated dienes were significantly reduced in fructose fed rats treated with TCW. Activities of antioxidant enzymes are up regulated significantly in TCW treated rats. Histopathological analysis of liver showed that TCW treatment reduced the lipid accumulation and inflammatory infiltration without any significant hepatocellular damage. **Conclusions:** The overall results suggest that, TCW treatment could prevent and reverse high blood pressure induced by high fructose diet probably by inhibition of lipid peroxidation, upregulation of antioxidant status and improved insulin sensitivity.

## 1. Introduction

The metabolic syndrome is associated with increased risk for type 2 diabetes and coronary heart disease[1]. This syndrome consists of a cluster of clinical abnormalities including dyslipidemia, specifically elevated triglycerides, insulin resistance and hypertension[2]. Several lines suggest that insulin resistance plays a key role in the development of metabolic syndrome and the hyperinsulinaemia and hyperlipidaemia may be a target for the treatment of this disease cluster[3].

Fructose has been implicated as a contributor to nearly all of the classic manifestations of the metabolic syndrome. Rats fed with high fructose diet provide an animal model of insulin resistance and acquired form of systolic hypertension[4]. Studies have shown that high dosage of fructose induces hyperinsulinemia, hypertriglyceridemia, impaired glucose tolerance and hypertension in rats[5]. In addition, fructose consumption in rats has pro-oxidant effects[6] and displays oxidative stress, an imbalance between free radical production and antioxidant defense in several tissues[7]. Oxygen radicals are known to produce membrane peroxidation and malondialdehyde formation[8]. Antioxidants prevent the organism from the harmful effects of free radicals by scavenging or inhibiting their formation[9]. A number of studies have reported that the supplementation of antioxidants improve insulin sensitivity in patients with insulin resistance[10], type 2 diabetes, hypertension and cardiovascular disease[11].

The recent trend worldwide has been in favor of phytochemical therapeutics as they are economical and largely free from adverse side effects. Much attention has been focused on plant foods that may be beneficial in preventing metabolic syndrome[12]. Dietary patterns high in fruits, vegetables and cereal content were generally

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found to be associated with lower incidence of metabolic syndrome[13]. Tender coconut water (TCW), which is the liquid endosperm, is widely consumed in tropical countries. TCW is the most nutritious wholesome beverage that the nature has provided. TCW is a natural isotonic beverage with almost the same level of electrolyte as we have in our blood. The richness of macro and micro nutrients in TCW are reported to have hypolipidemic, cardioprotective and hepatoprotective effects[14,15]. The therapeutic properties of tender coconut water made its usage as a remedy for a lot of ailments. Recent studies with TCW indicated that it is a rich source of cardioprotective factors viz., L-arginine[16], magnesium, potassium, calcium and vitamin C which are known to reduce the risk for coronary heart disease[15, 17].

Current therapies for hypertension normalize blood pressure by various means without removing the cause. Many of these treatments are prone to side effects which may result in poor compliance. The ideal treatment would be a natural compound that would reduce the cause of disease and could control blood pressure without side effects. Epidemiologic studies have suggested the associations between the consumption of antioxidants and the prevention of many human diseases. Antioxidants which occur naturally in the diet may be taken as dietary supplements which are essential to quench ROS[18]. Thus the present study was done to investigate the effects of tender coconut water (TCW) on oxidative stress and insulin resistance in experimentally induced hypertension in rats.

## 2. Material and methods

### 2.1. Animals

Male Sprague- Dawley rats weighing between 150 -170 g were used for the study. The rats were kept in a laboratory animal unit with a 12 hr light/dark cycle. Throughout the experiment, room temperature was maintained at (25 ± 2) ℃. The rats were maintained on a standard chow diet (Sai Feeds, Bangalore, India) and water *ad libitum* prior to dietary manipulation. They were trained for the first week to become acclimated to the procedure of indirect blood pressure measurement. The laboratory guidelines of the University Federation of Animal Welfare for the use and care of animals (1987) were followed throughout the experimental period.

### 2.2. Collection of tender coconut water

Young coconuts (*Cocos nucifera*) (West Coast Tall Variety) 5-6 months of age harvested from the coconut trees grown on the University campus were used for the study. The coconuts were, broken carefully and liquid endosperm was collected and used for the experiment.

### 2.3. Experimental design

After acclimatization the rats were divided into 4 groups of 6 rats each, and treated with the following methods:

Group I: Control

Group II: Control + TCW

Group III: Fructose fed rats

Group IV: Fructose + TCW

The first and second group of rats received the control diet containing 71% corn starch, 8% fat and 16% protein throughout the experiment. The third and fourth group received a diet containing 71% fructose, 8% fat and 16% protein. From the third week onwards the second and fourth group of rats received TCW (4 mL/100 g of body weight) by gastric intubation. All other rats received same volume of distilled water. The diets were prepared fresh daily. The animals were maintained in their respective groups for 42 days.

### 2.4. Blood pressure measurement

Systolic blood pressures (SBP) in conscious rats were measured using the non-invasive tail - cuff method. The animals were prewarmed at 30 ℃. The equipment used included magnetic animal holders connected with manual scanner (model 65-12, IITC, Inc; woodland hills, California, USA), pulse amplifier (model 59, IITC, Inc.), and dual-channel flat bed recorder (model L-1200-2, IITC). During the measurement seven individual readings were obtained. The highest and lowest readings were not considered and the average of the remaining five readings was retained. The systolic blood pressure (SBP) was measured every 3 days.

### 2.5. Biochemical analysis

At the end of the experiment, the animals were sacrificed by decapitation and blood samples were collected for biochemical determinations. Blood glucose and Serum triglyceride was estimated using reagent kit purchased from Agappe diagnostics Pvt Ltd. (Thane, Maharashtra, India). Serum free fatty acids were estimated by the method of Falholt et al (1973). Plasma insulin was assayed by enzyme - linked immunosorbent assay (ELISA) kit (BARC, Bombay, India). Activities of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd) and glutathione content (GC) were assayed in liver, heart, kidney and aorta. Protein content was estimated by the method of Lowry *et al*[19]. Malondialdehyde (MDA), hydroperoxides (HP) and conjugated dienes (CD) was assayed in different tissues. An HPLC method was used for the determination of plasma

vitamin E. concentration of plasma vitamin C was estimated spectrophotometrically.

### 2.6. Histopathological analysis

The liver tissues were rapidly dissected out and fixed by immersion at room temperature in 10% formalin solution. For the histological examinations, paraffin embedded tissue sections of liver were stained with hematoxylin – eosin (H&E). The tissue samples were then examined and photographed under a light microscope for observation of structural abnormality.

### 2.7. Statistical analysis

The SPSS statistical program was employed. The results were evaluated using analysis of variance (ANOVA) utilizing the F test. The results are presented as the mean value ± SD for the control and experimental rats. Differences among the means for the groups were assessed using the Duncans Multiple Range Test to determine which mean values were significantly different at $P<0.05$.

## 3. Results

Figure 1 shows weekly systolic blood pressure in control and experimental rats. All the groups of rats presented similar systolic blood pressure reading at the beginning of the experiment. The fructose– treated rats displayed a continuous increase in systolic blood pressure during the first three weeks from (119±2) mmHg to (145±2) mmHg ($P<0.05$). Administration of TCW during the subsequent weeks markedly reduced the blood pressure from (145±2) mmHg to (126±3) mmHg. Thus there was a progressive decrease in blood pressure from third week onwards.

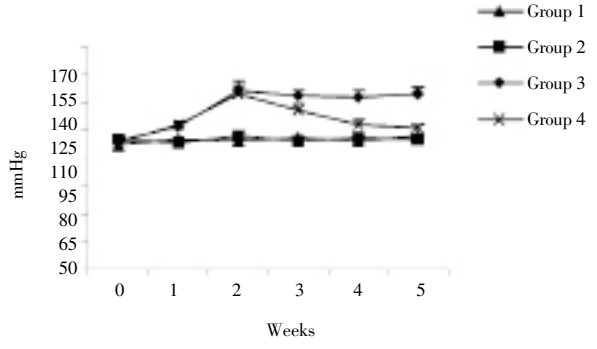


**Figure 1.** Effect of TCW on systolic blood pressure in control and fructose fed hypertensive rats.
Values are mean±SD for six rats in each group. $P<0.05$, [a] significantly different from control group, [b] significantly different from fructose group.

Table 1 indicates the effect of TCW on plasma insulin and glucose, serum triglyceride and free fatty acids in control and experimental groups. Plasma glucose and insulin, serum triglyceride and free fatty acids were significantly higher in fructose–fed rats whereas TCW administration decreased the plasma insulin and glucose, serum triglyceride and free fatty acids raised by high fructose diet.

Figure 2, 3 & 4 shows the levels of malondialdehyde (MDA), hydroperoxides (HP) and conjugated dienes (CD) in tissues (liver, heart, kidney and aorta) in control and experimental animals. Fructose fed rats showed significantly ($P<0.05$) higher levels of lipid peroxidation products when compared to control rats. Treatment with TCW decreased the levels of MDA, HP and CD near to normal and was significantly lower as compared with untreated fructose fed rats.

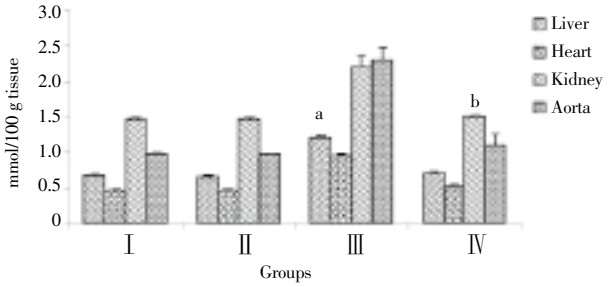


**Figure 2.** Concentration of malondialdehyde (MDA) in tissues of control and experimental animals.

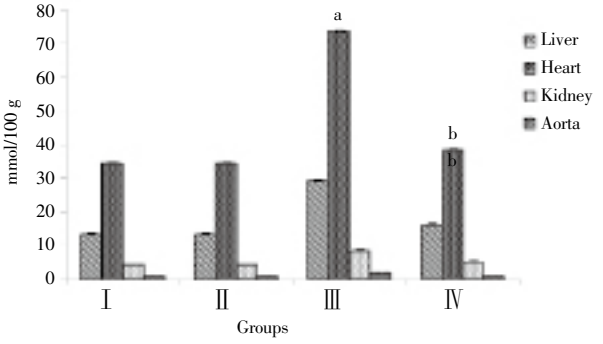


**Figure 3.** Levels of hydroperoxides (HP) in tissues of control and experimental animals.

Figure 5, 6, 7, 8 & 9 summarizes the activities of enzymatic antioxidants viz superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd) and glutathione content (GC) in the tissues (liver, heart kidney and aorta) of control and experimental animals. The activities of antioxidant enzymes were significantly decreased ($P<0.05$) in fructose–fed rats than control rats. Treatment with TCW in fructose fed rats showed elevated levels of antioxidant enzymes in tissues.

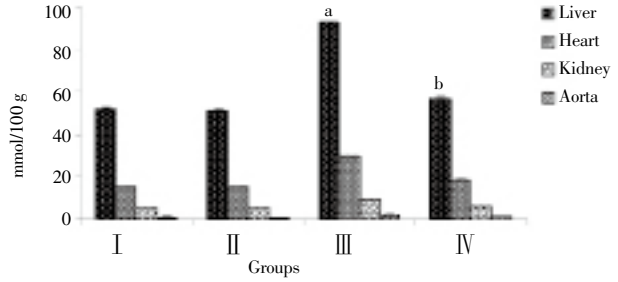


**Figure 4.** Levels of conjugated dienes (CD) in tissues of control and experimental animals.

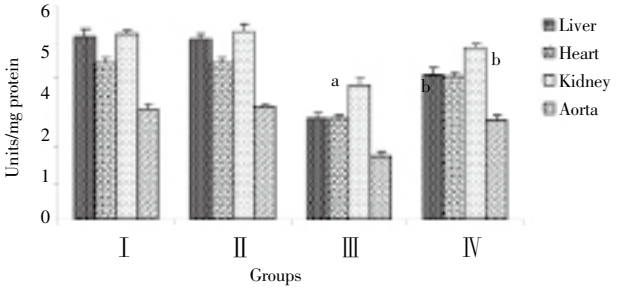


**Figure 5.** Activities of superoxide dismutase (SOD) in the tissues of control and experimental animals.
One unit is defined as the enzyme concentration required to inhibit the optical density at 560 nm of chromogen produced by 50% in one minute.

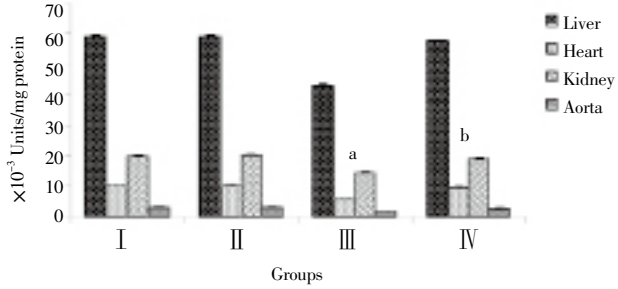


**Figure 6.** Activities of catalase (CAT) in the tissues of control and experimental animals.
One unit is defined as the velocity constant per second.

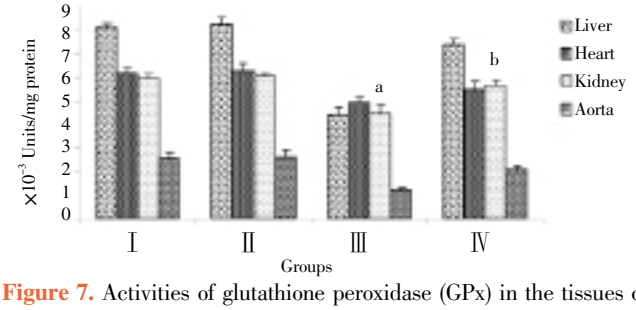


**Figure 7.** Activities of glutathione peroxidase (GPx) in the tissues of control and experimental animals.
One unit is defined as the μ mole of NADPH oxidized per minute.

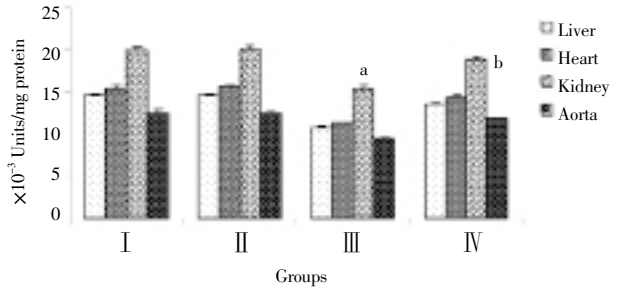


**Figure 8.** Activities of glutathione reductase (GRd) of control and experimental animals.
One unit is defined as the μ mole of NADPH oxidized per minute.

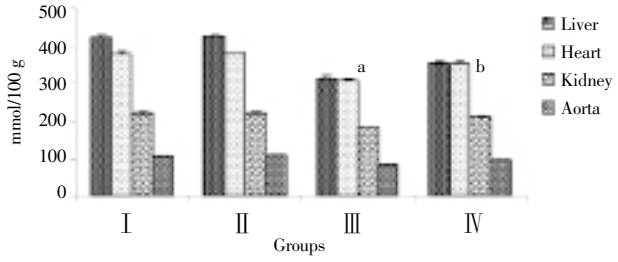


**Figure 9.** Concentration of reduced glutathione in the tissues of control and experimental animals.

Figure 10 represents the concentration of non-enzymatic antioxidants viz Vitamin C and Vitamin E in plasma of control and experimental animals. Significant ($P<0.05$) decrease in the concentration of antioxidant vitamins were observed in fructose-fed rats where as treatment with fructose fed rats with TCW brought the levels to near control values.

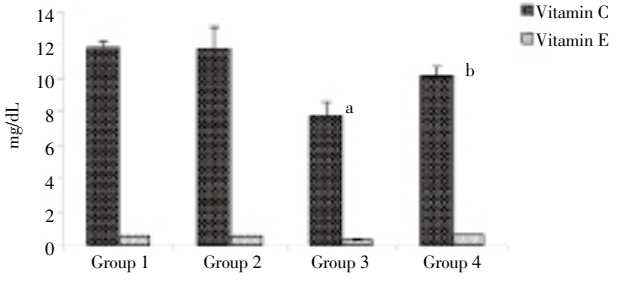


**Figure 10.** Concentration of vitamin C and vitamin E in plasma of control and experimental animals.

Histopathological analysis of the liver showed that (Figure 11) fructose feeding caused lipid accumulation, hepatocellular damage and inflammatory infiltration when compared to control rats. TCW treatment in fructose fed rats showed reduced lipid accumulation and with out any hepatocellular damage and inflammatory infiltration.

**Table 1**

Effect of TCW on plasma insulin, plasma glucose, serum triglycerides and serum free fatty acids in control and fructose-fed hypertensive rats.

| Parameters | Plasma insulin ( $\mu$ IU/mL) | Plasma glucose (mg/dL) | Serum triglycerides (mg/dL) | Serum free fatty acids (mg/dL) |
|---|---|---|---|---|
| Control | 21.00±1.09 | 86.48±3.20 | 7.10±0.90 | 71.65±2.63 |
| Control+ TCW | 22.00±1.64 | 89.20±1.20 | 6.91±1.10 | 69.6 0±3.50 |
| Fructose | 46.00±1.00[a] | 153.45±4.50[a] | 12.40±1.40[a] | 123.50±4.61[a] |
| Fructose+ TCW | 27.00±1.09[b] | 112.71±8.51[b] | 9.06±0.40[b] | 85.05±3.90[b] |

Values are mean ±SD for six rats in each group. $P<0.05$, significantly different from control groupa, significantly different from fructose groupb.

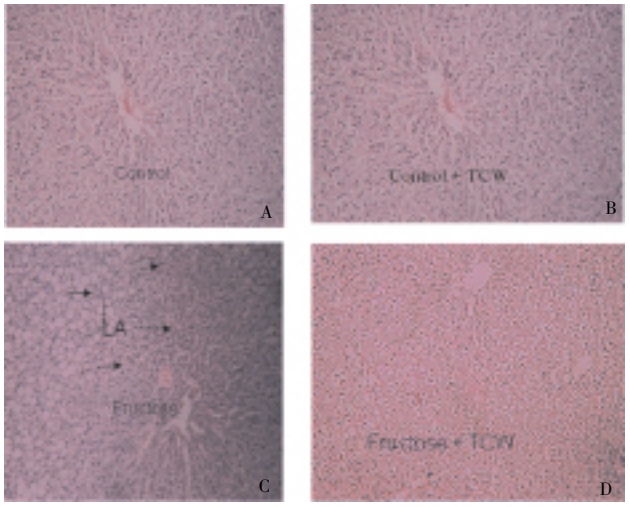


**Figure 11.** Histopathological analysis of the liver.

A. Control group: The liver architecture is normal with cords of hepatocytes with normal cytoplasm and central nuclei. No abnormal features; *B. Control* + TCW treated group: No hepatic damage and fatty infiltration. The liver architecture same as normal.

*C. Fructose* fed group: Liver of fructose fed rats showed degenerative changes, hepatocellular damage, inflammatory infiltration and cytoplasmic vacuolization (spherical vacuoles) accumulated with lipids (LA); D. Fructose fed + TCW treated group: TCW treatment in fructose fed rats showed no hepatocellular damage and inflammatory infiltration with lower lipid accumulation (LA).

## 4. Discussion

In the present study high fructose feeding resulted in hyperglycemia, hypertriglyceridemia and hyperinsulinemia which correlates with the results supported by other studies[20]. Subsequent findings suggest that the defects in glucose metabolism may play a role in the development of hypertension, dyslipidemia and coronary disease[21]. Hyperglycemia is well known to generate reactive oxygen species (ROS) and subsequent lipid peroxidation. Accumulating evidence indicates that hyperglycemia can cause the production of free radicals[22]. Enhanced lipid peroxidation in fructose-fed rats could be associated with high circulating glucose, which enhances free radical production from glucose autoxidation and protein glycation[23]. Hyperglycemia is generally accepted to cause vascular complications and the involvement of oxidative damage induced by glucose has been proposed in its pathogenesis[24].

Increase in plasma glucose level associated with hyperinsulinemia suggests impaired insulin action in fructose fed rats. Insulin resistance may occur due to a defect in insulin binding caused by decreased receptor number or affinity or defects at the level of effecter molecules such as glucose transporters and enzymes involved in glucose metabolism[25]. Studies have demonstrated that low levels of insulin stimulated glucose oxidation in the liver, skeletal muscle and adipose tissue in fructose-fed rats. Previous reports suggest that fructose feeding decreases the efficacy of insulin extraction by the liver, which retards insulin clearance from the circulation[26]. Hepatic metabolism of fructose leads to alterations in the activities of key enzymes of glucose metabolism and activation of stress sensitive pathways that may desensitize insulin signaling[27].

Free fatty acids (FFA) concentration was found to be elevated in the plasma of fructose-induced hypertensive rats. Lower levels of free fatty acids in serum suggest that the substrate availability for lipid peroxidation is less which correlates with the decreased levels of lipid peroxides. The lower level of lipid peroxides observed in TCW fed rats not only due to the reduction of FFA but also due to increased levels of free radical scavenging enzymes. Hypertriglyceridemia is another factor that could enhance the formation of lipid peroxides. It has been reported that lipid peroxide levels directly correlate with hypertriglyceridemia in diabetic patients[28]. In addition to this, fructose itself enhances the formation of ROS[29]. The lower levels of free fatty acids and triglycerides in TCW treated rats may be due to its hypolipidemic effects. Our previous studies have also found that TCW exhibits significant hypolipidemic and antihypertensive effects in fructose fed hypertensive rats[30].

Insulin has a regulatory effect on FFA metabolism[31]. A defect in the ability of insulin to regulate the free fatty acid metabolism could contribute to the increased free fatty acid levels. Plasma FFA levels remain higher in hypertensive than in control rats during hyperglycemia-induced hyperinsulinemia[32]. Increase in plasma FFA have demonstrated that the increase in plasma FFA concentration resulting from infusion of triglyceride emulsions has been shown to accelerate endogenous glucose production and cause fasting hyperglycemia in normal humans. Elevated levels of plasma FFA may play a key role in the pathogenesis of NIDDM by inhibiting peripheral glucose utilization and by promoting hepatic glucose overproduction[33]. FFA is an important substrates for hepatic triglyceride synthesis and a diminished suppression of plasma FFA by insulin leads to higher plasma triglyceride levels. The acute inhibitory effect of insulin on hepatic VLDL-lipoprotein secretion is modified by the ambient plasma FFA concentration[34].

In this study high fructose diet led to increased tissue lipid peroxidation in rats. Lipid peroxidation is a fundamental process in atherogenesis and hypertension. Lipid peroxidation products may contribute to tissue damage through direct cytotoxic actions on endothelial cells. In our study treatment with tender coconut water was able to decrease tissue lipid peroxides indicating that coconut water possess antioxidant property. Administration of TCW markedly lowered lipid peroxides viz MDA, HP and CD in the

liver, heart, kidney and aorta.

TCW treatment increased the activity of SOD and Catalase and it scavenges superoxide radicals and reduces oxidative stress. SOD scavenges superoxide radicals and reduces oxidative stress. SOD is an important antioxidant metallo enzyme that catalyzes very efficiently the dismutation of superoxide ions into oxygen and $H_2O_2$. SOD eliminates superoxide radical and thus protects the cells from damage induced by free radicals. Catalase activity increased in tissues with TCW treatment, indicating that administration of TCW help to lower hydrogen peroxide concentration and its decomposition and subsequently reduce oxidative stress. Fructose fed rats showed decrease in GC, GPx and GRd activities in tissues. Glutathione levels and activities of glutathione dependent enzymes were increased in rats treated with TCW. GPx and GRd are essential for maintaining the constant ratio of reduced glutathione to oxidized glutathione in cells. Decreased glutathione levels on fructose fed rats may be due to increased utilization for protecting sulfhydryl group of proteins from lipid peroxides. TCW feeding restores the glutathione level and increased the activities of GPx and GRd.

The increase in plasma lipid peroxides could also have resulted from a decline in cellular, non-enzymatic and enzymatic antioxidant potential in fructose-fed rats. The catalytic actions of antioxidant enzymes are important for the effective removal of oxygen radicals. Prolonged exposure of rats to hyperglycemic condition reduces the activities of antioxidant enzymes such as Catalase, Superoxide dismutase, Glutathione reductase and Glutathione peroxidase in fructose-fed rats as supported by studies. Free radical damage decreases the activities of antioxidant enzymes such as catalase, Glutathione Peroxidase and Superoxide dismutase[35] which have been reported to be reversed by vitamins in hypertension[36]. Modification of Cu-Zn Superoxide dismutase by glycation at specific lysine residue leads to inactivation and fermentation of the enzyme in the diabetic condition[37]. Reports are available that[38] catalase gene expressions are reduced in liver and heart of rats fed with fructose. Chemical characterization of tender coconut water revealed that it contains reducing sugar (4%), proteins (150 mg/dL), Sodium (40 mg/dL), potassium(220 mg/dL), calcium (40 mg/dL), magnesium (16 mg/dL), Selenium (0.01 mg/dL), L-arginine (30 mg/dL), vitamin C (30 mg/dL) and polyphenols (3.75 mg/dL). The superior effects of TCW in reducing oxidative stress in fructose fed rats are due to the presence of these biologically active compounds. Phenolic compounds are excellent free radical scavengers, exert significant antioxidant activities and thereby reduce oxidative stress. Vitamin C can directly scavenge singlet oxygen, superoxide and hydroxyl radicals. It reduces the risk of CVD by reducing blood pressure, blood cholesterol and the formation of oxidized LDL cholesterol[39]. Vitamin C is known to increase tissue glutathione, a storage form of cysteine which is reported to prevent hypertension[40]. Potassium is reported to be antihypertensive and increased dietary potassium can lower blood pressure in animals and humans[41]. Mg has been also reported to reduce free radical generation[42-49]. L- arginine has been reported to inhibit the generation of ROS and lipid peroxidation and act as an antihypertensive agent. There were reports that L-arginine has significant antioxidant, hypolipidemic, vasodilator and antiatherogenic effect[50]. Supplementation with L-arginine blocks the progression of plaques via restoration of NOS substrate availability and reduction of vascular oxidative stress supported by recent studies[51]. Histopathological studies of liver tissue also revealed the protective effect of tender coconut water against fructose induced tissue damage.

In conclusion, results of the present study shows that TCW treatment effectively reduced the oxidative stress in fructose fed hypertensive rats and improved the antioxidant status. The ability to bring a favorable metabolic environment and the antioxidant activity makes tender coconut water an ideal candidate for the treatment of clinical conditions associated with hypertension.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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