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Ameliorative effects of gallic acid on cardio-renal complexity induced by isoproterenol

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Abstract: Myocardial infarction (MI) arises out many risk factors, which work in concert and give rise to a lot of unfavorable outcome especially on the kidney. In the present study, we investigate the effect of gallic acid (GA), a natural antioxidant on cardio-renal complexity induced by isoproterenol (ISO). The myocardial infarcted rats showed deterioration in the heart function measured by lactate dehydrogenase (LDH) and creatin kinase (CK) and kidney function measured by urea, uric acid and creatinine. There were relative overweight in both the organs. Abnormal oxidation in lipids of their membrane indicated by the increased malomdialdhyde (MDA) content and nitrite level indicating the increase in their nitric oxide (NO). However, the result indicated a decrease in glutathione (GSH) content and superoxide dismutase (SOD) and peroxidase (POX) activities. These results were assured by other measurements as brain naturetic peptide (BNP) and myoglobin (Mgb) which indicated a damage happened in the myocytes, C-reactive protein (CRP) indicated the inflammatory response and homocystain, angiotensin and aldosterone levels which indicating the kidney hormones secretion. In conclusion, GA ascertained its efficacy in ameliorating the heart function biomarkers, kidney function testes and hormones and oxidation state.

Key wards: Isoproterenol; gallic acid; oxidative stress; cardio-renal complexity

Introduction

Heart failure (HF) and chronic kidney diseases (CKD) frequently co-exist, which can related to common risk factors, e.g. hypertension and atherosclerosis, and to common pathogenic mechanisms, such as the activation of the sympathetic nervous system, renin–angiotensin system, inflammation, and oxidative stress. Evidence also suggests that cardiac dysfunction may cause renal dysfunction, and vice versa[1]. In uremic patients, the morbidity and mortality of cardiovascular disease are substantially higher than in the general population[2].

Advancement in the understanding of the pathogenesis of atherosclerotic vascular disease suggests a central contribution of the inflammatory process. Epidemiological data have documented associations between C-reactive protein (CRP), the prototypical acute phase response protein, and cardiovascular disease in general population. It was suggested that it conceder a predictor of coronary events[3] and a risk marker for renal function loss[4]. Activity of the renin-angiotensin-aldosterone system (RAAS) is increased in patients with heart failure, and its maladaptive mechanisms may lead to adverse effects such as cardiac remodeling and sympathetic activation[5]. Angiotensin II plays a pivotal role in the development of renal cell proliferation and apoptosis in the setting of hypertension[6].

The appearance of cardiac hormones in the circulation generally indicates myocardial tissue injury[7]. The natriuretic peptide system, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C natriuretic peptide, is an important marker of cardiac failure. These peptides are synthesized in atrial or ventricular myocytes in response to wall tension. Several studies have demonstrated the correlation between high BNP levels and mortality in patients with acute coronary syndrome and heart failure. BNP could use, for instance, as an early diagnostic marker for the differential diagnosis between cardiogenic and non-cardiogenic dyspnea[8]. Another protein that may be useful for detecting skeletal muscle toxicity is myoglobin, an abundant heme-containing oxygen carrier expressed predominantly in cardiac fibers[9]. Like cardiac troponin, serum myoglobin is a clinically useful muscle injury biomarker[10].

Homocysteine is another risk factor that has attracted much interest among nephrologists. Senaratne *et al.*,[11] revealed that hyper-homocysteinemia is associated with an increased risk of cardiovascular diseases independently of classical risk factors and importantly, with early decline in renal function, which is common in atherosclerosis. Decline in renal function alone causes elevated plasma homocysteine. These observations suggest that mild hyper-homocysteinemia could often be an effect rather

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than a cause of atherosclerotic diseases[12]. Other reported that homocysteine evokes endothelial dysfunction and impairment of nitric oxide (NO) bioavailability in animal models[13] and cell culture studies[14]. There are multiple plausible mechanisms, by which this sulfur-containing amino acid may promotes endothelial dysfunction and vascular disease[15]. One possible mechanism of homocysteine's effects is the generation of hydrogen peroxide[16].

Plants constitute a vital source of active natural products, which differ widely in terms of structure and biological properties. Lastly, the prevention of cardiovascular diseases has been associated with ingestion of fresh fruits, vegetables or plants rich in natural antioxidants. The protective effects of plants can be due to the presence of flavonoids[17], anthocyanin and other phenolic compounds[18]. In this context, gallic acid (GA) received much attention because of its potent free radical scavenging and antioxidant actions[19]. Gallic acid (3,4,5-trihydroxybenzoic acid) is found particularly abundant in green teas[20]. Various biological activities of GA have been reported, as it possesses strong antioxidant, anti-inflammatory, antimutagenic and anticancer activities[21], antibacterial[22], antiviral[23], antiapoptotic activities and diabetic hypolipidemic effect[24]. It was reported that to ameliorate the early diabetic nephropathy in rats[25].

From the fact that, cardiac and renal are associated diseases, the current experiment was designed to evaluate the treating effect of GA on the cardiovascular action to protect the kidney and vice versa.

Material and Methods

Animals

Investigation was performed on white male albino rats (*Rattus norvegicus*), weighing 160-200gm. The animals were acclimatized under standard laboratory conditions of temperature and humidity with a normal photoperiod of 12 hours' light and dark cycle for seven days.

Chemicals and induction of myocardial infarction

We purchased isoproterenol (ISO) and gallic acid (GA) from Sigma (St Louis, MO, USA). All other chemicals were of the highest grade commercially available. Myocardial infarction was induced by subcutaneous (Sc) injection of 150 mg/kg/b.w. isoproterenol hydrochloride, dissolved in physiological saline (0.9 NaCl) and given on two consecutive days.

The studied groups

40 rats were randomly divided into four groups:

1. Control group, injected subcutaneously with normal saline.
2. Control group, injected subcutaneously with gallic acid (15 mg/ kg b.wt.)[26].
3. Myocardial infarcted group, rats injected with isoproterenol
4. Treated group, rats injected with isoproterenol and then treated for two weeks with gallic acid (15 mg/ kg b.wt.)[26] dissolved in normal saline and given by gastric intubation.

Sample preparation

At the end of the experimental period, rats were scarified; blood was collected and centrifuged for serum separation, which is stored at -20°. Kidney and heart were fast removed, washed, weighted then frozen until homogenizing in saline for preparing homogenate measurements

Biochemical assay measurements:

Lactate dehydrogenase (LDH) and creatine phosphokinase (CK) activities were determined by the method of Young[27] and Anbarasi *et al.,*[28], respectively. Pyruvate kinase activity was assayed essentially as described by Leong *et al.,*[29]. Moreover, Bibbins-Domingo *et al.,*[30] determined the method used for the determination of brain-type natriuretic peptide (BNP). Cartledge and Lawson[31] identified the method of aldosterone measurement, while angiotensin was measured according to the method of Varagic *et al.,*[32] C-reactive protein (CRP) was measured according to the method of Hattori *et al.,*[33]

Kidney function biomarkers concentrations as, serum urea was determined according to the method of Kaplan[34], uric acid was determined according to the method of Fossati *et al.,*[35] and creatinine was determined by kinetic method of Young[36]. In addition, total proteins concentration was determined according to the method of Peters *et al.,*[37] and albumin was determined by the method of Doumas *et al.,*[38]

Oxidative stress biomarkers in the kidney homogenate were determined by measuring lipid peroxidation according to the chemical method of Preuss *et al.,*[39] while nitric oxide (NO) level according to the method of James and Glaven[40]. The antioxidant biomarkers measured are peroxidase enzyme (POX) activity, which was determined according to the chemical method of Kar and Mishra[41], superoxide dismutase (SOD) by Marklund and Marklin[42] method and glutathione content was determined, with some modifications, referring to the procedure of Beutler *et al.,*[43]

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) Statistical Package for Social Science (SPSS) version 20. Results were expressed as mean ± SE. from six

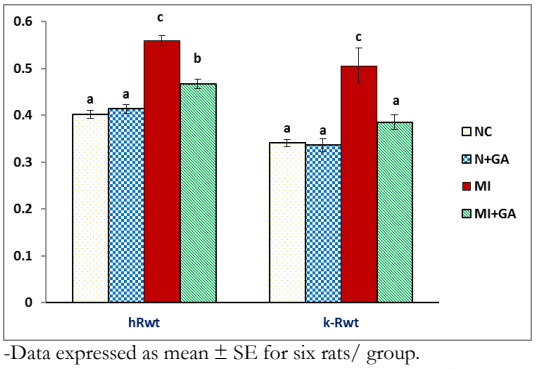
rats in each group. Having p values <0.05 were considered as significant.

Results

Organs hypertrophic response to isoproterenol induction

Figure 1 indicates changes in relative heart and kidney relative weight after ISO induction. The ISO treated group (MI) recorded a significant increase (P<0.001) in the relative weight of the two organs in comparison to the normal ones. The normal groups (NC and N+GA) recorded the lowest relative heart weight followed by the MI group treated with GA (MI+GA), while there was no significant variation between normal and treated groups of the kidney relative weight.

Figure 1: Effect of gallic acid treatment on heart and kidney relative weight in myocardial infarcted rats.



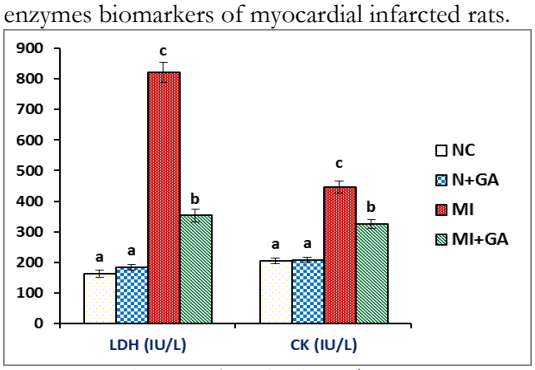
-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Cardiac function biomarkers

The myocardial dysfunction in the present study was indicated in figure 2, there was an observed elevation of LDH and CK in ISO injected rats compared to the normal control measurements. After GA treatment, there was a significant amelioration (P<0.001). Treatment of GA alone in the normal rats showed no significant change in comparison to the normal ones. Figure 3 indicated the change in pyruvate kinase activity in the heart homogenate with an inverse behavioral manner to the previous enzymes, as the lowest activity was observed in the ISO injected group in accordance to the normal control group, the normal GA treated group and myocardial infarcted GA treated group.

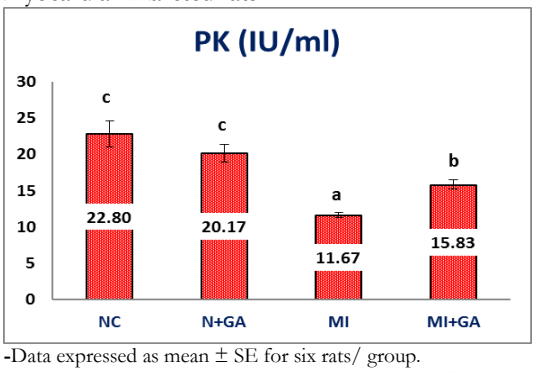
Figure 4 illustrated another cardiac failure marker, BNP with the highest level recorded in the myocardial infarcted group, then lowered after GA treatment and the lowest level recorded in the normal, GA treated group. The muscle toxicity detecting protein, myoglobin, showed the reverse behavior to the previous measurements as it recorded the lowest value in the myocardial infarcted rats and the highest value recorded in the normal, GA treated group (Figure 5). Figures 6 and 7 indicated the obvious elevated level in homocysteine, a vascular dysfunction indicator, and C- reactive protein, an inflammatory indicator, after ISO injection and ameliorated after GA treatment while normal GA treated group showed no significant change (P>0.05) compared to the normal control ones.

Figure 2: Effect of gallic acid treatment on serum enzymes biomarkers of myocardial infarcted rats.



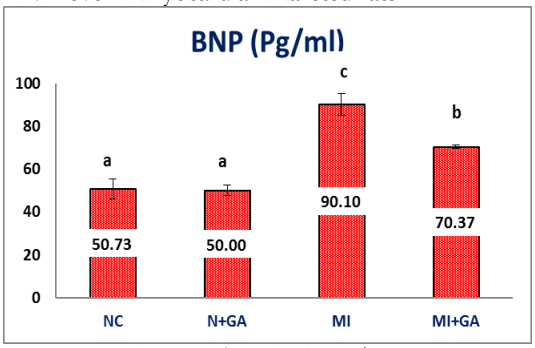
-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Figure 3: Effect of gallic acid treatment on pyruvate kinase activity in the heart tissue of myocardial infarcted rats.



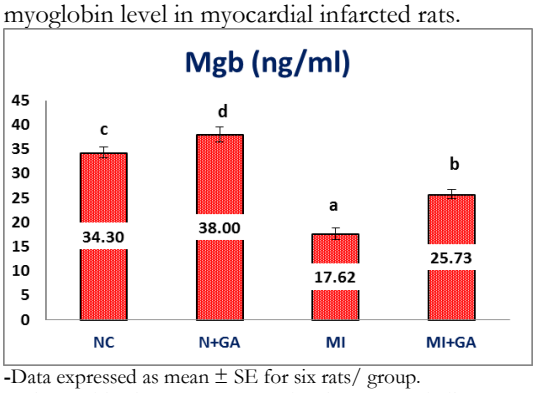
-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Figure 4: Effect of gallic acid treatment on serum BNP level in myocardial infarcted rats.



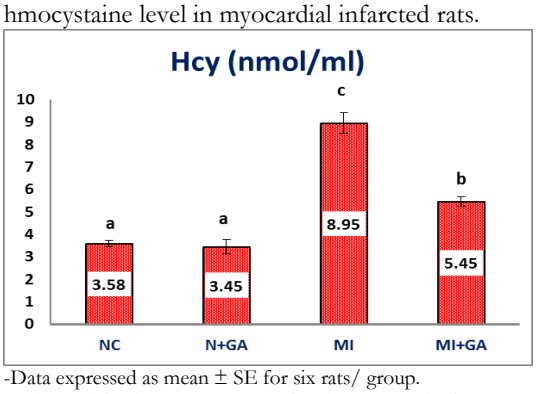
- Data expressed as mean ± SE for six rats/ group.
- Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Figure 5: Effect of gallic acid treatment on serum myoglobin level in myocardial infarcted rats.



-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Figure 6: Effect of gallic acid treatment on serum hmocystaine level in myocardial infarcted rats.



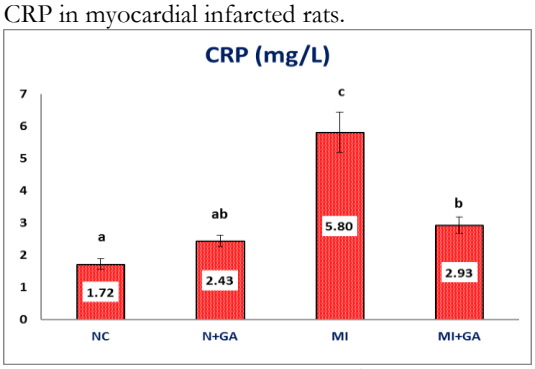
-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Renal function biomarkers

Angiotensin and aldosterone levels elevated markedly (P<0.001) after ISO injection and ameliorated after GA treatment in comparison to the control group (Figure 8).

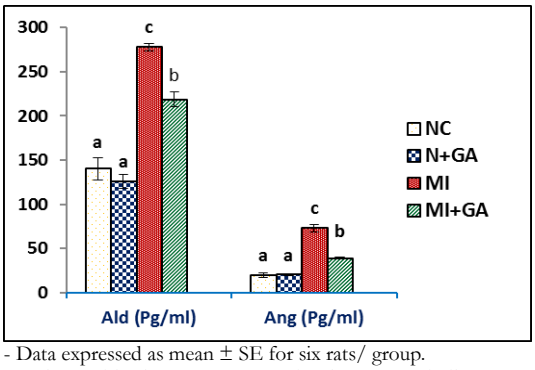
Table 1 indicate the renal biomarkers measurement, there was an observed elevation in creatinine, urea, and uric acid levels in induced rats. However, their restoration was observed in rats treated with gallic acid (P<0.001). Serum total protein and serum albumin decreased significantly in the myocardial infarcted rats and improve after GA treatment.

Figure 7: Effect of gallic acid treatment on serum CRP in myocardial infarcted rats.



-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Figure 8: Effect of gallic acid treatment on serum aldosterone and angiotensin levels in myocardial infarcted rats.



- Data expressed as mean ± SE for six rats/ group.
- Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Table 1: Effect of gallic acid treatment on serum biomarkers of kidney function in myocardial infarcted rats.

Groups	Urea (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)	Total protein (g/dl)	Albumin (g/dl)
NC	40.00 ± 2.921^{a}	1.328 ± 0.084^{a}	0.323 ± 0.025^{a}	6.500 ± 0.203^{c}	3.700 ± 0.228^{c}
N+GA	34.00 ± 2.394^{a}	1.340 ± 0.048^{a}	0.348 ± 0.025^{a}	7.233 ±0.463^{c}	3.686 ± 0.219^{c}
MI	72.667 ± 1.054^{c}	2.997 ± 0.141^{c}	0.698 ± 0.071^{b}	3.433 ± 0.112^{a}	2.100 ± 0.036^{a}
MI+GA	55.500 ± 1.335^{b}	2.105 ± 0.149^{b}	0.482 ± 0.019^{a}	4.633 ± 0.117^{b}	2.990 ± 0.037^{b}

- Data expressed as mean ± SE for six rats/ group.
- Values with the same superscript letter are (non-significantly different (P > 0.05).

Oxidation biomarkers

The oxidative stress is measured by lipid peroxidation expressed by the of MDA content and nitric oxide expressed by the amount of nitrite formed, as indicators of oxidation process while the antioxidant mechanism is measured by the activity of superoxide dismutase activity and glutathione content (Table 2). Both the heart and the kidney had parallel oxidation or antioxidant response. GA expressed a significant reduction (P<0.001) in MDA and nitrite content after MI induction. GA was also efficient in increasing the antioxidant expressing markers after their

significant decrease (P<0.001) in the myocardial infarction group compared to the normal control ones. On the other hand, GA did not significantly change the oxidation mechanism when intubated to the normal rats.

Table 2: Effect of gallic acid treatment on oxidation biomarkers in heart and kidney homogenate of myocardial infarcted rats.

Groups	LPn (nmol MDA /g tissue)		NO (nmol nitrite /g tissue)		SOD (U/g tissue)		GSH (µmol/g tissue)	
	Heart	Kidney	Heart	Kidney	Heart	Kidney	Heart	Kidney
NC	188.333±3.073[a]	104.500±9.043[a]	124.240±3.548 [a]	130.388±6.009[a]	3.900±0.224 [bc]	2.129±0.032 [bc]	8.137±0.240 [c]	6.693±0.465[c]
N+GA	179.333±3.073 [a]	128.50±4.807 [ab]	112.00±4.575 [a]	120.167±5.109 [a]	4.367±0.308 [c]	2.360 ± 0.145 [c]	8.300±0.412 [c]	6.933±0.276 [c]
MI	383.333±7.601 [c]	259.667±25.82[c]	245.224±13.450 [c]	291.427±12.969[c]	2.400±0.132 [b]	1.228 ± 0.127 [a]	2.683±0.220 [b]	2.565±0.249[a]
MI+GA	254.00±10.066 [b]	184.500±9.639[b]	148.62±1.479 [b]	186.533±12.377[b]	3.300±0.183 [a]	1.933 ± 0.056[b]	4.847±0.049[a]	4.067±0.112[b]

-Data expressed as mean ± SE for six rats/ group.
-Values with the same superscript letter are (non-significantly different (P > 0.05).

Discussion

Heart failure may cause kidney dysfunction through multiple mechanisms. These mechanisms can be subdivided into haemodynamic (measured by increased serum creatinine), neurohormonal, inflammatory and oxidative stress mechanism[1]. The kidney dysfunction was proved here by the elevated levels of urea, uric acid or creatinine in MI group.

In this study, MI was induced in rats by subcutaneous administration of isoproterenol in a dose of 75 mg/kg for two successive days. It has been reported that acute induction of isoproterenol to animals produces infarct like lesions in the heart similar to those present in MI in humans[44]. Mechanisms suggested to explain isoproterenol-induced cardiac damage were varied and comprise generation of highly cytotoxic free radicals, increased calcium overload, and mitochondrial injury or dysfunction[45,46]. In the present study, there was an increase in cardiac and renal MDA content (an indicator for lipid peroxidation) due to of decreased antioxidant enzyme and decreased, free radical scavenger, GSH content in ISO induced group. These results were in line with the work of some investigators[45,47].

An elevation in nitrite content was observed in the present study after isoproterenol injection. Nitric oxide (NO) has been implicated in the depression of cardiac function in human heart failure. Some reports have identified inducible nitric oxide synthase (iNOS) within the myocyte component of the failing human heart, and NO is known to decrease the contraction amplitude of isolated ventricular myocytes[48]. Isoproterenol revealed to increase iNOS expression[48]. Anker and von Haehling[49] also referred the high levels of NO production to iNOS and this cause dilated cardiomyopathy and congestive heart failure which is proved to increase with the increase in inflammatory mediators. Endothelium-derived NO is also widely recognized as a mediator of vasodilatation with important anti-inflammatory and antithrombotic properties[50].

Isoproterenol-generated free radicals initiate peroxidation of membrane-bound polyunsaturated fatty acids leading to damage of the structural and functional integrity of the myocardium with consequent changes in membrane permeability[51]. Myocyte death or altered membrane permeability causes the cytosolic contents to eventually enter the systemic circulation, where they may be detected as markers of the ischemic heart disease. This accounts for the elevation of serum activity of LDH and CK several hours following isoproterenol administration which was in accordance with many previous reports[52, 53, 54].

The last regulatory step of the glycolytic pathway is catalyzed by pyruvate kinase (PK) the decreased level of this enzyme may referred to its consumption in the ischemic myocytes. In the case of anaerobic respiration and in tissues which lack mitochondria, pyruvate is converted to lactic acid by LDH which is the enzyme involved in the final step of anaerobic glycolysis. It reflects the NAD+/NADH ratio, indicated by the lactate/pyruvate ratio in the cytosol. In addition to LDH, plasma CK activity is a more sensitive indicator in early stage of myocardial ischemia[55]. It catalyzes the transfer of phosphate from creatine phosphate to adenosine diphosphate (ADP), producing ATP.

The increased cardiac output and blood pressure during stress after ISO induction affects the sympathetic system which is frequently associated with pressure overload from hypertension or volume overload. Increased wall stress in the heart triggers a hypertrophic response that initially reflects a compensatory response turns into pathological cardiac and renal hypertrophy[56]. Hypertrophy may be referred to many possibilities firstly to accumulation of water content in the intramuscular space and by necrosis of cardiac muscle fibers[57]. In addition, it may be due to increased protein synthesis and invasion of inflammatory cells in necrotic tissue[58]. Ciccarelli *et al.,*[59] explained the hypertrophic response to the increased glucose uptake in heart along with increased oxidative stress after ISO administration.

Inflammation is a key process involved in mediating myocardial tissue damage after an ischemic event. In the current study, isoproterenol produced an increase in the inflammatory mechanism which was measured by serum CRP level, that is in accordance with the work of other investigators[60,61]. Although CRP was initially believed to be only a marker of vascular inflammation, it also plays an active role in atherogenesis. Hirschfield and Pepys[62] confirmed the presence of CRP selectively bound just LDL and some VLDL (coronary related lipids) in atheromatous plaques. Early inflammatory processes related to high body fat may predispose the kidney to glomerular hyperfiltration-related renal function loss[4].

The release of BNP reflects the alterations in left ventricular potency as a response to B-adrenergic stimulation result from ISO effects on the heart. These effects are mediated through B-1 and B-2 adrenoceptors, mediating the positive inotropic and chronotropic effects of B adrenoceptor agonists[63].

Atherogenesis and elevation of blood pressure commonly develop silently long time before the emergence of clinically evident vascular events. These processes also lead to nephrosclerosis and a degree of deterioration of renal function[64], and this is highly relevant to the plasma clearance of Hcy[65]. Hcy is toxic to the vascular endothelium. It impairs endothelial function[66] by inhibiting the synthesis of endothelium derived relaxing factor and nitric oxide. Hcy also increases their degradation via the generation of oxygen-derived radicals such as superoxide radical, peroxynitrite and hydrogen peroxide, which promote the growth of vascular smooth muscle, modification of proteins and peroxidation of lipids resulting in formation of oxidized low-density lipoprotein which can impair expression of nitric oxide synthase and directly degrade nitric oxide[67].

The increase in angiotensin level can explained by the increased activity of renin–angiotensin system due to increasing angiotensin I converting enzyme secondary to isoproterenol induction[68]. It is well known that aldosterone, that is elevated here, plays a vital role in heart failure, causing retention of sodium and water, promotion of myocardial fibrosis, reduced vascular compliance, and the development of malignant ventricular arrhythmia and it may not only synthesized and secreted in the zona glomerulosa of the adrenal cortex, but also within the heart itself[69].

Since consumption of pharmaceutical products has complications and problems, GA as a natural potent antioxidant found in many plants, fruits and herbs such as tea, red grapes and grape seed extract have been studied as a medical agent to treat many diseases. Anti-oxidants are substances that delay or inhibit oxidative damage to the target molecule and activate the cellular antioxidant system, both enzymatic and non-enzymatic defenses to counteract the reactive oxygen species (ROS)[70]. Treatment with GA increased the levels of reduced glutathione and antioxidant enzymes in the kidney and heart tissue of isoproterenol induced cardiotoxic rats, proving its antioxidant property. This is reported by Mansouri *et al.,*[71] who attributed its antioxidant effect in Parkinson's, as it was able to clean ROS, e.g. superoxide anions, hydrogen peroxide and hydroxyl radicals. From the point of view that proper endothelial function and vasorelaxation are important physiological phenomena related to many cardiovascular diseases[72], GA is considered as vasorelaxant via mechanism related to NO[73].

A significant decrease in LDH and CK activities and preservation of PK were observed after treatment with GA, this was supported by many authors. As they proved that GA treatment inhibited the leakage of these cardiac marker enzymes in the serum, referring to its antioxidant activity. GA treatment decreased the activities of lysosomal enzymes in the myocardium by its inhibitory effect on lipid peroxidation, thereby reducing the extent of lysosomal damage induced by isoproterenol in cardiotoxic rats[26,72]. Treatment with GA significantly reduced the relative organs weights this might be due to the reversal of stress induced adrenomedullary response. Kang *et al.,*[73] explained the ameliorated effect of GA on angiotensin II and aldosterone levels by it inhibiting effect on angiotensin-I converting enzyme.

Conclusion

The above data indicated that GA ascertained its efficacy by ameliorating the heart function biomarkers, kidney function testes and hormones and oxidation state. Therefore, it has amelioration effects in the cardio-renal indices.

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