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Combined effect of tyramine and phlorizin on isoproterenol induced myocardial infarction in wistar rats

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Abstract

This study aims to investigate the combined effect of Tyramine and Phlorizin on lipid peroxides, Antioxidant enzymes and membrane bound enzymes in isoproterenol induced myocardial infarction were studied in Wistar rats. Pretreatment with Tyramine and Phlorizin at different doses of 10, 20 and 30 mg/kg to isoproterenol (85mg/kg) treated rats significantly prevented the altered lipid peroxides, antioxidant enzymes and membrane bound enzymes to near normal status. The results of our study showed that the cardio protective potential of Tyramine and phlorizin on isoproterenol induced myocardial infarction, due to its antioxidant and free radical scavenging effects, maintains the defense system against cardiac damage.

Keywords: Tyramine, phlorizin, myocardial infarction, isoproterenol, lipid peroxides and antioxidants

Introduction

Cardiovascular disease like myocardial infarction (MI) affects a major proportion of the population. MI occurs as a result of imbalance between coronary blood supply and myocardial demand ^[1]. Isoproterenol, a catecholamine causes severe infarction in heart tissue. Isoproterenol-induced MI has been reported to show many metabolic and morphologic alterations in the heart tissue of the experimental animals, similar to those observed in human Myocardial infarction ^[2]. Dietary factors plays an important role in various human disease including cardiovascular disease. Phlorizin is naturally occurring in some plants. It could be found in the bark of pear (*Pyrus communis*), apple, cherry and other fruit trees (Rosaceae) and is responsible for the petal color in *Dianthus caryophyllus*. Phlorizin belongs to a class of polyphenols. It has a wide variety of pharmacological activities such as antioxidant and anti-inflammatory activity mainly acting as a free radical scavenger, due to the presence of hydroxyl groups ^[3]. Tyramine is also naturally occurring in plants and animals. Tyramine is present in relatively high concentrations in fermented foods such as cheese, sausage, pepperoni, salami, pickled or smoked fish & yeast supplements. Small amounts are found in red wine & chicken liver as well ^[4].

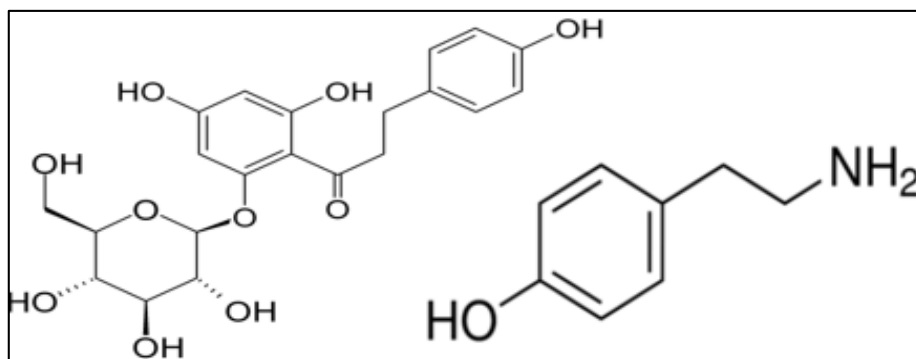


Fig 1: Structure of Phlorizin

Fig 2: Structure of Tyramine

However no systematic studies were found to be done on combined effect of Tyramine and Phlorizin on experimental animal model of Myocardial infarction. Hence, the present study was aim to evaluate the cardio protective combined effect of Tyramine and Phlorizin on lipid peroxide metabolism, antioxidant and membrane bound enzyme activity on Isoproterenol induced Myocardial infarction in male albino wistar rats.

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Materials and methods

Experimental animals and diet

The experiments were carried out according to the guidelines of the Committee and approved by the Institutional animal ethical committee (IAEC/XLI/03/CLBMCP/2017). All the experiments were done with a healthy male albino wistar rats weighing 150-180 g. They were housed in polypropylene cages (47 cm x 34 cm x 20 cm) lined with husk, renewed every 24 h under a 12:12 h light dark cycle at around 22 °C. The rats had free access to tap water and food. The rats were fed on a standard pellet diet (Pranav Agro Industries Ltd., Maharashtra, India). The pellet diet consisted of 22.02% crude protein, 4.25% crude oil, 3.25% crude fibre, 7.5% ash, 1.38% sand silica, 0.8% calcium, 0.6% phosphorus, 2.46% glucose, 1.8% vitamins and 56.17% nitrogen free extract (carbohydrates). The diet provided a metabolisable energy of 3000 kcal.

Drug and chemicals

Tyramine was purchased from TCI Chemicals Company, Chennai. Phloridzin and Isoproterenol had been purchased from Sigma Aldrich Company, Deisenhofen, Germany. All the other chemicals used in this study were of analytical grade and obtained from E.MERCK and HIMEDIA, India.

Induction of experimental myocardial infarction

Isoproterenol (85 mg/kg) was dissolved in normal saline and subcutaneously injected to rats at intervals of 24 h for 2 days.

Experimental design

The rats were divided into 8 groups of 6 rats in each group were used for the experiment.

Group I: Normal control rats

Groups II: Normal rats were treated with Tyramine & Phloridzin (10 mg/kg).

Group III: Normal rats were treated with Tyramine & Phloridzin (20 mg/kg).

Group IV: Normal rats were treated with Tyramine & Phloridzin (30 mg/kg).

Group V: ISO control rats (85 mg/kg).

Group VI: Rats were pretreated with Tyramine & Phloridzin (10 mg/kg) and then subcutaneously injected with ISO.

Group VII: Rats were pretreated with Tyramine & Phloridzin (20 mg/kg) and then subcutaneously injected with ISO.

Group VIII: Rats were pretreated with Tyramine & Phloridzin (30 mg/kg) and then subcutaneously injected with ISO.

Tyramine 0& Phloridzin was dissolved in DMSO (10%) and administered to rats orally using an intra gastric tube daily for a period of 21 days. Blood was collected and serum separated by centrifugation. The heart tissue was excised immediately from the animals, washed off blood with ice-chilled physiological saline. A known weight of the heart tissue was homogenized in 5.0 ml of 0.1 M Tris-HCl buffer (pH 7.4) solution. The homogenate was centrifuged and the supernatant was used for the estimation of various biochemical parameters.

Biochemical estimations

The activity of thiobarbituric acid reactive substances (TBARS) was estimated by the methods of Yagi^[5] and Fraga et al.,^[6]. The values were expressed as nM/ml and mM/100g wet tissue. The levels of lipid hydroperoxides were estimated by the method of Jiang et al.,^[7]. Values were expressed as $\times 10^{-5}$ mM/dL for plasma and mM/100g wet tissue for heart. The activities of superoxide dismutase (SOD) was assayed according to the procedure of Kakkar et al.,^[8]. The activity of SOD was expressed as units/mg protein. The activities of catalase (CAT) were assayed by the methods of Sinha^[9], the activity of catalase was expressed as μmol of H_2O_2 consumed/min/mg protein. The activities of glutathione peroxidase (GPX), glutathione reductase (GRX) and glutathione-S-transferase (GST) Rotruck et al.,^[10], Horn and Burns.,^[11] and Habig and Jakoby.,^[12], respectively. The levels of reduced glutathione (GSH), vitamin C, vitamin E and ceruloplasmin were estimated by the methods of Ellman^[13], Omaye et al.,^[14], Baker et al.,^[15] and Ravin^[16], respectively. The activities of Na^+/K^+ -ATPase, Ca^{2+} -ATPase, Mg^{2+} -ATPase was assayed according to the procedure of Bonting (1970)^[17], Hjerten and Pan (1983)^[18] and Ohnishi *et al.* (1982)^[19], respectively. The content of protein in the heart homogenate was determined by the method of Lowry et al.,^[20].

Statistical Analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) using Statistical Package for the Social Sciences (SPSS) software package version 17.00. Results were expressed as mean \pm SD for five rats in each group. *P* values < 0.05 were considered significant.

Results

Table-1 shows the levels of TBARS and LOOH in plasma and the heart of normal and experimental rats. Rats induced with ISO showed a significant ($P < 0.05$) increase in the levels of TBARS and LOOH in plasma and the heart compared to normal control rats. Oral pretreatment with Tyramine & phloridzin (10, 20 and 30 mg/kg) to ISO-induced rats daily for a period of 21 days significantly ($P < 0.05$) decreased the levels of TBARS and LOOH in plasma and the heart compared with ISO-alone induced rats.

Table 1: Combined Effect of Tyramine and Phloridzin on the levels of Thiobarbituric acid reactive substances (TBARS) and Lipid hydroperoxides (LOOH) in plasma and the heart of normal and isoproterenol (ISO) induced myocardial infarction in rats.

Groups	Normal control	Normal + Tyramine & phlorizin (10mg/kg)	Normal + Tyramine & phlorizin (20mg/kg)	Normal + Tyramine & phlorizin (30mg/kg)	ISO (85mg/kg) alone	Tyramine & phlorizin (10mg/kg) + ISO	Tyramine & phlorizin (20mg/kg) + ISO	Tyramine & phlorizin (30mg/kg) + ISO
Plasma TBARS (n MOL/ml)	5.5 ± 0.3 ^a	5.6 ± 0.3 ^a	5.7 ± 0.3 ^a	5.8 ± 0.3 ^a	10.1 ± 0.7 ^b	8.9 ± 0.7 ^c	7.5 ± 0.6 ^d	6.8 ± 0.4 ^c
Heart TBARS (m MOL/100g wet tissue)	0.9 ± 0.1 ^a	0.9 ± 0.1 ^a	0.9 ± 0.1 ^a	0.9 ± 0.1 ^a	2.8 ± 1.3 ^b	2.4 ± 1.1 ^c	2.0 ± 0.9 ^d	1.7 ± 0.6 ^e
Plasma LOOH (values x 10 ⁻⁵ m MOL/Dl)	14.2 ± 1.1 ^a	14.2 ± 1.1 ^a	14.2 ± 1.1 ^a	14.2 ± 1.1 ^a	22.4 ± 1.8 ^b	19.3 ± 1.6 ^c	17.1 ± 1.4 ^d	15.1 ± 1.2 ^e
Heart LOOH (m MOL/100g wet tissue)	21.5 ± 1.7 ^a	21.5 ± 1.7 ^a	21.5 ± 1.7 ^a	21.5 ± 1.7 ^a	43.5 ± 4.1 ^b	39.5 ± 3.5 ^c	32.5 ± 2.9 ^d	24.2 ± 2.2 ^e

Each value is mean ± SD for six rats in each groups; values not sharing a common superscript (a, b, c, d, e) differ significantly with each other ($P < 0.05$, DMRT).

Table-2 depicts the levels of GSH in Plasma and heart, GSH-PX, GST and GSH-Rx in heart. Rats were induced with Isoproterenol (85mg/kg) shows a significantly ($P < 0.05$) decrease in the activities of enzymatic antioxidants when compared with normal control rats. Pretreatment with

Tyramine & phlorizin (10, 20 and 30 mg/kg) to ISO-induced rats shows significant ($P < 0.05$) increase the activities of the enzymatic antioxidants, when compared to Isoproterenol induced rats.

Table 2: Combined Effect of Tyramine and Phloridzin on the activities of Glutathione peroxidase (GPx), Glutathione reductase (GRX) and Glutathione-S-Transferase (GST) in heart and Reduced Glutathione (GSH) in plasma and the heart of normal and isoproterenol (ISO) induced myocardial infarction in rats.

Groups	Normal control	Normal+ Tyramine & phlorizin (10mg/kg)	Normal + Tyramine & phlorizin (20mg/kg)	Normal + Tyramine & phlorizin (30mg/kg)	ISO (85mg/kg)	Tyramine & phlorizin (10mg/kg) + ISO	Tyramine & phlorizin (20mg/kg) + ISO	Tyramine & phlorizin (30mg/kg) + ISO
GPX (µg of GSH Consumed/min/mg protein)	4.5 ± 0.3 ^a	4.5 ± 0.4 ^a	4.5 ± 0.3 ^a	4.6 ± 0.4 ^a	1.0 ± 0.2 ^b	1.84 ± 0.1 ^c	2.83 ± 0.1 ^d	3.78 ± 0.1 ^e
GRX (n MOL of NADPH oxidized/ min/100mg protein)	6.4 ± 0.5 ^a	6.4 ± 0.5 ^a	6.5 ± 0.5 ^a	6.53 ± 0.5 ^a	2.8 ± 0.3 ^b	2.98 ± 0.3 ^c	3.7 ± 0.3 ^d	4.95 ± 0.4
GST(NMOL of CDNB conjugated/min/mg protein)	751.0 ± 1.9 ^a	753.1 ± 70.5 ^a	759.2 ± 70.2 ^a	758.1 ± 70.8 ^a	478.8 ± 40.1 ^b	571.5 ± 52.2 ^c	652.4 ± 52.7 ^d	701.5 ± 67.1 ^e
Plasma GSH (mg/Dl)	27.4 ± 1.9 ^a	27.5 ± 1.7 ^a	27.7 ± 1.7 ^a	27.9 ± 1.8 ^a	8.9 ± 0.9 ^b	10.9 ± 1.3 ^c	13.7 ± 1.3 ^d	16.3 ± 1.5 ^e
Heart GSH (MMOL/GWET tissue)	8.1 ± 0.6 ^a	8.1 ± 0.6 ^a	8.1 ± 0.6 ^a	8.16 ± 0.7 ^a	3.5 ± 0.3 ^b	4.5 ± 0.4 ^c	5.6 ± 0.4 ^d	6.4 ± 0.5 ^e

Each value is mean ± SD for six rats in each groups; values not sharing a common superscript (a, b, c, d, e) differ significantly with each other. ($P < 0.05$, DMRT).

Figure 3- shows the activities of SOD and catalase in the heart of normal and experimental rats. In ISO-treated rats, the activities of these enzymes were declined significantly ($P < 0.05$) in the heart when compared to normal rats. Pretreatment

with Tyramine & phlorizin (10, 20 and 30 mg/kg) to ISO-induced rats significantly ($P < 0.05$) increased the activities of these enzymes when compared to ISO-alone induced rats.

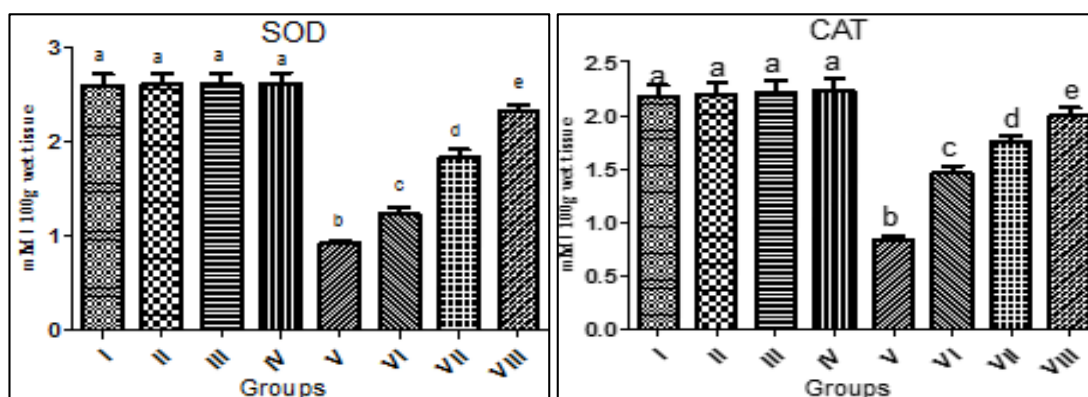
**Fig 3:** Combined Effect of Tyramine and Phloridzin on the activities of Superoxide Dismutase (SOD) and Catalase in the heart of normal and isoproterenol (ISO) induced myocardial infarction in rats. Each value is mean ± SD for six rats in each groups; values not sharing a common superscript (a, b, c, d, e) differ significantly with each other ($P < 0.05$, DMRT).

Table 3- shows the levels of vitamin C and vitamin E in plasma and the heart in normal and ISO-induced rats. Rats induced with ISO exhibited significantly ($P < 0.05$) decrease in the levels of vitamin C and E in plasma and the heart, when compared with normal control

rats. Oral administration of Tyramine & phlorizin (10, 20 and 30 mg/kg) to ISO-induced rats significantly ($P < 0.05$) increased the levels of vitamin C and E in plasma and the heart in plasma when compared to ISO-alone induced rats.

Table 3: Combined Effect of Tyramine and Phloridzin on the levels of Vitamin C, Vitamin E in plasma and the heart and the levels of Protein in the heart of normal and isoproterenol (ISO) induced myocardial infarction in rats (ISO) induced myocardial infarction in rats.

Groups	Normal control	Normal + Tyramine & phlorizin (10mg/kg)	Normal + Tyramine & phlorizin (20mg/kg)	Normal + Tyramine & phlorizin (30mg/kg)	ISO (85mg/kg) alone	Tyramine & phlorizin (10mg/kg) + ISO	Tyramine & phlorizin (20mg/kg) + ISO	Tyramine & phlorizin (30mg/kg) + ISO
Plasma vitamin C (mg/Dl)	2.7 ± 0.2 ^a	2.7 ± 0.3 ^a	2.7 ± 0.3 ^a	2.9 ± 0.5 ^a	0.9 ± 0.1 ^b	1.4 ± 0.1 ^c	1.9 ± 0.2 ^d	2.3 ± 0.2 ^e
Heart vitamin C (MMOL/mg protein)	1.4 ± 0.1 ^a	1.4 ± 0.2 ^a	1.4 ± 0.3 ^a	1.5 ± 0.4 ^a	0.4 ± 0.05 ^b	0.5 ± 0.1 ^c	0.8 ± 0.1 ^d	1.1 ± 0.1 ^e
Plasma Vitamin E (mg/Dl)	4.4 ± 0.1 ^a	4.4 ± 0.2 ^a	4.4 ± 0.3 ^a	4.4 ± 0.4 ^a	0.9 ± 0.5 ^b	1.7 ± 0.1 ^c	2.4 ± 0.1 ^d	3.7 ± 0.2 ^e
Heart vitamin E (MMOL/mg protein)	0.7 ± 0.1 ^a	0.7 ± 0.2 ^a	0.7 ± 0.3 ^a	0.76 ± 0.4 ^a	0.3 ± 0.1 ^b	0.4 ± 0.1 ^c	0.54 ± 0.1 ^d	0.62 ± 0.1 ^e

Each value is mean ± SD for six rats in each groups; values not sharing a common superscript (a, b, c, d, e) differ significantly with each other ($P < 0.05$, DMRT).

Figure-4 shows the effect of Tyramine and Phloridzin on the activities of Na^+/K^+ ATPase, Ca^{2+} and Mg^{2+} ATPases in normal and ISO-induced rats. The activity of Na^+/K^+ ATPase was decreased significantly ($P < 0.05$) and the activities of Ca^{2+} and Mg^{2+} ATPases were increased significantly ($P < 0.05$) in the heart of ISO-induced rats when compared to normal control rats. Tyramine and Phloridzin (10, 20, and 30 mg/kg) pretreatment to ISO-induced rats significantly ($P < 0.05$) increased the activity of Na^+/K^+ ATPase and significantly ($P < 0.05$) decreased the activities of Ca^{2+} and Mg^{2+} ATPases in the heart compared to ISO-alone induced rats.

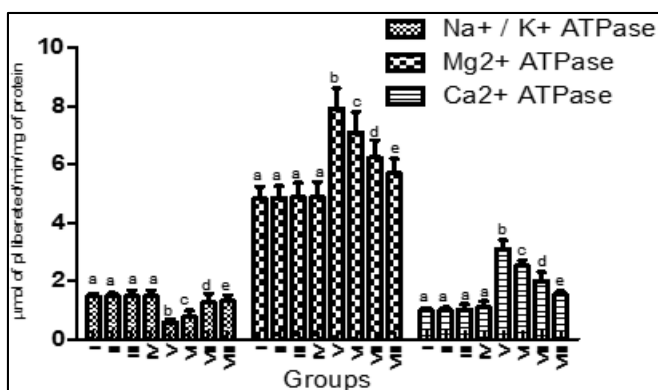


Fig 4: Combined Effect of Tyramine and Phloridzin on the levels of Na^+/K^+ ATPase, Ca^{2+} and Mg^{2+} ATPases in the heart of normal and isoproterenol (ISO) induced myocardial infarction in rats (ISO) induced myocardial infarction in rats. Each value is mean ± SD for six rats in each groups; values not sharing a common superscript (a, b, c, d, e) differ significantly with each other ($P < 0.05$, DMRT).

Discussion

In this study, Tyramine and Phloridzin have been found to have various pharmacological properties like antidiabetic, antifungal, lipid lower effect, anticancer, anti-inflammatory, antibacterial, antidepressant, free radical scavenging and antioxidant effects. Thus in this study, we have studied the combined effect of Tyramine and Phloridzin on normal and ISO induced myocardial infarcted rats.

Lipid peroxidation is an important pathogenic event that hurts myocardial membrane. Increased lipid peroxidation is thought to be a consequence of oxidative stress, when the dynamic balance between pro-oxidant and antioxidant mechanism is impaired [21]. Lipid peroxidation *in vivo*, has been identified as the basic deteriorative reactions in cellular mechanisms

during myocardial infarction [22]. In present study, subcutaneous injection of ISO caused significant elevated levels of TBARS and LOOH, due to oxidative stress in experimentally induced myocardial injury. However, pretreatment with Tyramine and Phloridzin decreased the levels of TBARS, LOOH in ISO-induced rats. This anti-lipid peroxidation effect of Tyramine and Phloridzin may be responsible for its membrane stabilizing effect. Elevation of lipid peroxides in ISO-induced rats could be attributed to the accumulation of lipids in the heart and irretrievable damage to the myocardial membranes. Increased levels of lipid peroxidation products injure blood vessels. Our results are in agreement with a previous report [23]. Tyramine and Phloridzin pretreated ISO administered rats, maintained the levels of lipid peroxides to near normal in plasma and the heart. This is due to the inhibitory effect of tyramine and phloridzin on lipid- peroxidation [24].

SOD, Catalase, and GPX are the primary free radical scavenging enzymes involved in cellular defense against oxidative injury, removing O_2 and H_2O_2 before they can interact to form more hydroxyl radicals [25]. In this study, the ISO treated rats showed a significant decrease in the heart. However pretreatment with Tyramine and Phloridzin shows an increased in the activities of the enzymes. The observed decrease in the activities of these enzymes may be due to increased ROS generation. This in turn leads to inactivation of these enzymes and results in decreased removal of superoxide radicals, H_2O_2 , and highly potent hydroxyl radicals. In Myocardial infarction, the production of superoxide radicals and H_2O_2 inactivates SOD and catalase resulting in the loss of activity and accumulation of superoxide anion and H_2O_2 , thus damaging the myocardial cell [28]. However oral pre-treatment with Tyramine and Phloridzin on ISO-induced rats showed significant elevation in the activities of these enzymes in heart. Thus, Tyramine and Phloridzin scavenges superoxide radicals and hydrogen peroxide produced by ISO and reduces myocardial damage. GRX is an antioxidant enzyme involved in the reduction of (GSSG) glutathione (an end product of the GPX reaction) to glutathione (GSH) [29]. In this study, a significant decline in the concentration of GSH in the heart was observed in ISO-induced rats, indicating that depletion of GSH resulted in enhanced lipid peroxidation, and excessive lipid peroxidation caused increased GSH consumption [30]. Prior administration of Tyramine and Phloridzin resulted in significant elevation of GSH, which indicates the protection

offered by Tyramine and Phloridzin against ISO-induced myocardial injury. The activities of GSH-dependent antioxidant enzymes (GPX, GST and GRX) were decreased in ISO-treated hearts. The lowered activities of GPX and GST in heart of ISO- treated rats are due to reduced availability of GSH.

Reduced glutathione (GSH) is one of the most important endogenous anti-oxidants, which play a key role against free radical damage. The decrease levels of GSH decreases the activities of glutathione dependent enzymes such as GPX and GST in ISO-induced rats. Decreased availability of GSH also reduces the activities of GPX and GST in ISO-induced MI. In this study, the activities of GPX and GST were significantly decreased in ISO-induced rats, along with reduction in the levels of GSH in plasma and heart. Our observations are in correlation with previous report^[31].

Vitamin E is the major lipid-soluble antioxidant present in cell membranes and lipoproteins that defends against oxidative modification. The major antioxidant of the aqueous phase is vitamin C, which acts as the first line of defense during oxidative stress^[32]. In this study, there is a lowered levels of Vitamin C and Vitamin E in plasma and the heart of ISO treated rats. However pre-treatment with Tyramine and Phloridzin significantly increased the levels of Vitamin C and Vitamin E. The observed decrease in vitamin E and vitamin C might be due to increased utilization for the neutralization of ISO-mediated free radicals and lipid peroxidation. Tyramine and Phloridzin pre-treatment showed marked increase in vitamin C and vitamin E levels in ISO induced rats. The previous study reported that the cardioprotective effects of vitamin E may be due to its beneficial effect in reducing excess tissue aldehydes. Vitamin C reduces the risk of CVD by reducing cholesterol, BP and the formation of oxidized LDL. Pre-treatment to ISO-induced rats significantly increased the levels of Vitamin C and E in plasma and heart of ISO-induced rats^[33].

The activities of membrane bound enzymes such as Na⁺/ K⁺ ATPase, Ca²⁺ATPase and Mg²⁺ATPase maintain the mitochondria membrane integrity. ATPase of the cardiac cells play a significant role in the contraction and relaxation of cycles of the cardiac muscles by maintaining normal ion levels (Ca²⁺, Na⁺, Mg²⁺) within the myocytes. Cellular injury is associated with alterations in ionic homeostasis. Thus, these enzymes and ions play a vital role in the pathology of myocardial infarction. There is a decrease in the activity of Na⁺/K⁺-ATPase and increase in the activities of Ca²⁺ and magnesium dependent adenosine triphosphatase (Mg²⁺-ATPase) in ISO-induced rats. The inhibition of sodium potassium dependent adenosine triphosphatase (Na⁺/K⁺-ATPase) can activate the Na⁺-Ca²⁺ exchange mechanism in the myocardium. This Na⁺-Ca²⁺ exchange mechanism may play a vital role in regulating the cellular calcium levels^[34]. The Calcium dependent adenosine triphosphatase (Ca²⁺-ATPase) is the major active calcium transport protein responsible for the maintenance of normal intracellular calcium levels in a variety of cell types. In the heart, cytosolic calcium is carefully controlled and Ca²⁺ is the key ion for normal activity of many enzymes^[35].

In the present study, a significant decrease in the activity of Na⁺ /K⁺ ATPase and significant increase in the activities of Ca²⁺ and Mg²⁺ATPases were observed in the hearts of ISO-induced MI rats. However in oral pre-treatment with Tyramine and Phloridzin there is an increase in Na⁺ / K⁺ ATPase and significant decrease in the activities of Ca²⁺ and

Mg²⁺ ATPase. This effect may be due to membrane stabilizing properties of Tyramine and Phloridzin.

Conclusion

The present study showed the combined effects of Tyramine and Phloridzin on ISO induced MI in wistar rats. In the present study Tyramine and Phloridzin also scavenges superoxide and hydroxyl radicals. Tyramine and Phloridzin were found to exhibit antioxidant in ISO-induced myocardial infarcted rats. Our results showed that Tyramine and Phloridzin possesses free radical scavenging, antioxidant and membrane stabilizing properties in both *in vivo* and *in vitro* studies. However, further clinical trials are needed before Tyramine and Phloridzin could be developed as a potential drug for various diseases.

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