Cardiovascular pharmacology

(−) Epicatechin prevents alterations in lysosomal glycohydrolases, cathepsins and reduces myocardial infarct size in isoproterenol-induced myocardial infarcted rats

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1. Introduction

Myocardial infarction is an important feature resulting in increased levels of mortality and morbidity. Myocardial ischemia occurs when myocardial oxygen demand exceeds oxygen supply and as a result it causes cell injury known as myocardial infarction (Mohanty et al., 2004). Pharmacological induction of myocardial infarction by subcutaneous administration of isoproterenol in animals like rats has been found to be convenient because of relatively smaller size of coronary arteries. Isoproterenol causes severe stress in the myocardium; resulting in infarct like necrosis of the heart muscle (Sushamakumari et al., 1989). It generates free radicals and stimulates lipid peroxidation, which is an important causative factor for irreversible damage to the myocardial membranes.

A lot of scientific studies support the theory that bioactive flavonoids have a potent role in the prevention of cardiovascular diseases. (−) Epicatechin is a member of a group of polyphenolic compounds collectively known as catechins, belonging to flavonoid family. It is a constituent of grape seeds, grape skin tannins, tea tannins, cocoa flavonoids, cola nuts, strawberries and red wine. The preventive effects of (−) epicatechin on oxidative stress, cardiac mitochondrial damage, altered membrane bound adenosine triphosphatases and minerals were reported previously in isoproterenol-induced myocardial infarction model. Leakage of lysosomal glycohydrolases and cathepsins play an important role in the pathology of myocardial infarction. This study was aimed to evaluate the preventive effects of (−) epicatechin on alterations in lysosomal glycohydrolases, cathepsins and myocardial infarct size in isoproterenol-induced myocardial infarcted rats. Male albino Wistar rats were pretreated with (−) epicatechin (20 mg/kg body weight) daily for a period of 21 days. After the pretreatment period, isoproterenol (100 mg/kg body weight) was injected subcutaneously into the rats at an interval of 24 h for two days to induce myocardial infarction. The levels of serum cardiac troponin-I and the activities of serum and heart lysosomal enzymes (β-glucuronidase, β-N-acetyl glucosaminidase, β-galactosidase, cathepsin-B and cathepsin-D) were increased significantly (P < 0.05) and the activities of β-glucuronidase and cathepsin-D in the heart lysosomal fractions were significantly (P < 0.05) decreased in isoproterenol-induced myocardial infarcted rats. The in vitro study revealed the potent antioxidant action of (−) epicatechin. Pretreatment with (−) epicatechin daily for a period of 21 days prevented the leakage of cardiac marker, lysosomal glycohydrolases, cathepsins, and reduced infarct size, thereby protecting the lysosomal membranes in isoproterenol-induced myocardial infarcted rats, by virtue of its membrane stabilizing property.

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lysosomes to the cytosol leads to myocardial cellular injury and death in the ischemic state of the heart (Riccutti, 1992). Also, alterations in the activity of lysosomal enzymes have been noticed in patients with myocardial infarction (Welman et al., 1978). Lysosomal destabilization may be prevented either by inhibition of cellular peroxidation or by prevention of iron catalyzed oxidative reactions, which involve peroxidation of cellular membranes, energy depletion and leakage of lysosomal content (Karthikeyan et al., 2007). It is possible that stabilization of myocardial cell membranes, particularly the lysosomal membranes, may prolong the viability of ischemic cardiac muscle and prevent myocardial infarction. Since lysosomal enzyme leakage is implicated in the pathogenesis of myocardial infarction, the inhibition of lysosomal leakage promises to be an extremely important target for therapeutic intervention. The concept of early therapeutic interference with pretreatment to prevent myocardial infarction and to protect lysosomes is extremely attractive. In continuation of the research on (-) epicatechin, the present investigation was aimed to evaluate whether pretreatment with (-) epicatechin exerts preventive effects against isoproterenol-induced changes in lysosomal lipid peroxidation, lysosomal glycosidases, cathepsins and myocardial infarct size in rats. The in vitro study on the antioxidant effect of (-) epicatechin was also determined.

2. Materials and methods

2.1. Chemicals

(-) Epicatechin, isoproterenol hydrochloride, p-nitrophenyl-N-acetyl-β-D-glucosaminide, sodium dodecyl sulphate, p-nitrophenyl-β-D-glucuronide and 2,2’-dinitrophenyl-6-sulfonic acid) radical were purchased from Sigma Chemical Co., St. Louis, MO, USA. All the other chemicals used in this study were of analytical grade.

2.2. In vivo study

2.2.1. Experimental animals and diet

Male albino Wistar rats (Rattus norvegicus) weighing 180–200 g, obtained from the Central Animal House, Rajah Muthiah Institute of Health Sciences, Annamalai University, Tamil Nadu, India were used in this study. They were housed in polypropylene cages (47 × 34 × 20 cm) lined with husk, renewed every 24 h under a 12:12 h light and dark cycle at around 22 °C. The rats had free access to tap water and food. They were fed on a standard pellet diet (Pranav Agro Industries Ltd., Maharashtra, India). The experiment was performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, New Delhi, India and approved by the Animal Ethical Committee of Annamalai University.

2.2.2. Induction of experimental myocardial infarction and experimental design

Isoproterenol (100 mg/kg body weight) was dissolved in saline and injected subcutaneously into rats at an interval of 24 h for two days to induce myocardial infarction (Stanely Mainzen Prince, 2011). The development of myocardial infarction at this dose was confirmed by elevated level of serum cardiac troponin-I in Wistar rats. The rats were randomly divided into four groups of eight rats each. Group I: Normal control rats; Group II: Rats were orally treated with (-) epicatechin (20 mg/kg body weight) daily for a period of 21 days by an intragastric tube; Group III: Rats were injected subcutaneously with isoproterenol alone (100 mg/kg body weight) at an interval of 24 h for 2 days (on 22nd and 23rd day); Group IV: Rats were orally pretreated with (-) epicatechin (20 mg/kg body weight) daily for a period of 21 days by an intragastric tube and then injected subcutaneously with isoproterenol (100 mg/kg body weight) at an interval of 24 h for 2 days (on 22nd and 23rd day). Normal control and isoproterenol control rats were orally given 1 mL of saline alone daily for a period of 21 days using an intragastric tube. (-) Epicatechin was dissolved in saline and administered to rats 1 mL each. The dose and duration of pretreatment of (-) epicatechin was fixed based on the earlier study (Stanely Mainzen Prince, 2011).

At the end of the experimental period, after 12 h of second isoproterenol injection (i.e. on 24th day), all the rats were anesthetized with high dose of pentobarbital sodium (60 mg/kg body weight) and then sacrificed by cervical decapitation. Blood was collected in dry test tubes without anticoagulant for serum. Heart tissues were excised immediately, rinsed in ice-chilled saline and tissue homogenates were prepared in suitable buffers for the estimations/assays of various biochemical parameters. All the enzyme assays were done immediately.

2.2.3. Separation of lysosomal and cytosolic fractions

The heart tissue samples were cut open and placed in isotonic saline to remove the blood. Then, the heart tissues were rinsed in ice cold 0.25 M sucrose at 4 °C. A portion of this preparation was used to determine the total activity of lysosomal enzymes. Another portion of the homogenate was subjected to differential centrifugation and the lysosomal and cytosolic fractions were separated by the following standard procedure: structural proteins, nucleus, and cell debris at 600 × g for 10 min; mitochondria at 5000 × g for 10 min; lysosomes at 15,000 × g for 10 min; microsomes at 120,000 × g for 30 min and supernatant, the cytosol. The myocardial lysosomal and cytosolic fractions were treated with Triton X-100 (final concentration 0.2% v/v) in ice for 15 min prior to the assay of enzymatic activities.

2.2.4. Estimation of cardiac sensitive marker

The level of serum cardiac troponin-I was estimated by electro chemiluminescence immunoassay using a standard kit (Roche Diagnostics, Switzerland).

2.2.5. Estimation/assays of lysosomal thiobarbituric acid reactive substances and enzymes

Thiobarbituric acid reactive substances in the lysosomal fraction of the heart were estimated by the method of Fraga et al. (1988). All the enzyme assays were done by standard methods. The activities of β-glucuronidase in the serum, heart tissue homogenate, lysosomal and cytosolic fractions were assayed according to the method of Kawai and Anno (1971). The activities of β-N-acetyl glucosaminidase, β-galactosidase and cathepsin-B in the serum and heart tissue homogenate were assayed by the methods of Moore and Morris (1982), Conchie et al. (1967) and Barrett (1972), respectively. Cathepsin-D activities in the serum, heart tissue homogenate, lysosomal and cytosolic fractions were assayed by the method of Sapolsky et al. (1973). Further, the content of protein in the heart tissue homogenate was estimated by the method of Lowry et al. (1951).

2.2.6. Determination of myocardial infarct size and quantification by cumulative planimetry

The determination of the size of infarcted myocardium was done according to the method of Lie et al. (1975). The heart tissues were transversely cut across the left ventricle to obtain slices not more than 0.1–0.2 mm in thickness. Then the tissue slices were kept in a prewarmed solution of 2,3,5 triphenyl tetrazolium chloride and heated to 37–40 °C for 45 min in an incubator. Finally, the heart
tissue slices were fixed and colored photographs were taken. Normal myocardium (lactate dehydrogenase enzyme active) turned to bright red, infarcted myocardium turned to uncolored and fibrous scars turned to white. The infarct size percentage was calculated in each individual heart slice by cumulative planimetry using image tool for windows (Version 2.0) software.

2.3. In vitro study

2.3.1. Total antioxidant activity of (−) epicatechin

The total antioxidant potential of (−) epicatechin was determined in vitro by the 2, 2′-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) radical scavenging method, as described by Miller et al. (1996).

2.4. Statistical analysis

Statistical analysis was performed by one way analysis of variance followed by Duncan’s multiple range test using Statistical package for the Social Science software package version 12.00. Results were expressed as mean ± standard deviation for eight rats in each group. P values < 0.05 were considered significant.

3. Results

Fig. 1 shows the activities of serum β-glucuronidase, β-N-acetyl glucosaminidase, β-galactosidase, cathepsin-B and cathepsin-D in normal and isoproterenol-induced myocardial infarcted rats. The activities of these enzymes were significantly (P < 0.05) increased in the serum of isoproterenol-induced myocardial infarcted rats (Group III) compared to normal control rats (Group I). Oral pretreatment with (−) epicatechin (20 mg/kg body weight) daily for a period of 21 days significantly (P < 0.05) decreased the activities of these enzymes in the serum of isoproterenol-induced myocardial infarcted rats (Group IV) compared to isoproterenol alone induced myocardial infarcted rats (Group III).

Fig. 2 depicts the activities of β-glucuronidase, β-N-acetyl glucosaminidase, β-galactosidase, cathepsin-B and cathepsin-D in the total heart of normal and isoproterenol-induced myocardial infarcted rats. The activities of these enzymes were significantly (P < 0.05) increased in the heart of isoproterenol-induced myocardial infarcted rats (Group III) compared to normal control rats (Group I). Pretreatment with (−) epicatechin (20 mg/kg body weight) significantly (P < 0.05) decreased the activities of these enzymes in the total heart of isoproterenol induced myocardial infarcted rats (Group IV) compared to isoproterenol-alone induced myocardial infarcted rats (Group III).

The activity of β-glucuronidase was significantly (P < 0.05) decreased in the lysosomal fraction of the heart and significantly (P < 0.05) increased in the cytosolic fraction of the heart in isoproterenol induced myocardial infarcted rats (Group III) compared to normal control rats (Group I). Pretreatment with (−) epicatechin (20 mg/kg body weight) significantly (P < 0.05) increased the activity of β-glucuronidase in the lysosomal fraction of the heart and significantly (P < 0.05) decreased the activity of this enzyme in the cytosolic fraction of the heart in isoproterenol induced myocardial infarcted rats (Group IV) compared to isoproterenol-alone induced myocardial infarcted rats (Group III) (Fig. 3).

The activity of cathepsin-D was significantly (P < 0.05) lowered in the lysosomal fraction of the heart and significantly (P < 0.05) increased in the cytosolic fraction of the heart in isoproterenol-induced myocardial infarcted rats (Group III) compared to normal control rats (Group I). Pretreatment with (−) epicatechin (20 mg/kg body weight) significantly (P < 0.05) increased the activity of cathepsin-D in the lysosomal fraction of the heart and significantly (P < 0.05) decreased the activity of this enzyme in the cytosolic fraction of the heart in isoproterenol-induced myocardial infarcted rats (Group IV) compared to isoproterenol alone induced myocardial infarcted rats (Group III) (Fig. 4).

Isoproterenol induced myocardial infarcted rats (Group III) showed significant (P < 0.05) increased levels of thiobarbituric acid reactive substances in the lysosomal fraction of the heart compared to normal control rats (Group I). Pretreatment with (−) epicatechin (20 mg/kg body weight) significantly (P < 0.05) decreased the levels of thiobarbituric acid reactive substances in isoproterenol induced myocardial infarcted rats (Group IV) compared to isoproterenol alone induced myocardial infarcted rats (Group III) (Fig. 5).

Isoproterenol-induced myocardial infarcted rats (Group III) showed considerable (P < 0.05) increased levels of serum cardiac troponin-I (2.51 ± 0.21 ng/mL) compared to normal control rats (0.21 ± 0.02 ng/mL) (Group I). Pretreatment with (−) epicatechin (20 mg/kg body weight) considerably (P < 0.05) lowered the levels of serum cardiac troponin-I (0.42 ± 0.03 ng/mL) in isoproterenol-induced myocardial infarcted rats (Group IV) compared to

![Fig. 1. Activities of lysosomal enzymes in the serum. Each column is mean ± standard deviation for eight rats in each group; NS as compared to normal control; *P < 0.05 as compared to normal control; †P < 0.05 as compared to ISO control, (Duncan’s multiple range test ); $NS—not significant. Units: β-glucuronidase: μmoles of p-nitrophenol liberated/h/mL serum; β-N-acetyl glucosaminidase: μmoles of p-nitrophenol liberated/h/mL serum; β-galactosidase: μmoles of p-nitrophenol liberated/h/mL serum; cathepsin-B: μmoles of p-nitroaniline liberated/h/mL serum; cathepsin-D: μmoles of tyrosine liberated/h/mL serum; EC: (−) epicatechin, ISO: isoproterenol.]
isoproterenol alone induced myocardial infarcted rats (Group III). Rats treated with (−) epicatechin (20 mg/kg body weight) (0.20 ± 0.02 ng/mL) did not show any considerable (P < 0.05) change in serum cardiac troponin-I levels (Group II).

In preclinical studies, the histological analysis is still considered to be the gold standard for measuring myocardial infarct size. Thus, slices of heart tissue of all groups of rats were examined for infarct size. The heart slices of normal (Group I)
and (−) epicatechin (20 mg/kg body weight) treated rats (Group II) revealed completely viable tissue (with red color), indicates the presence of lactate dehydrogenase and intact myocardial tissue (Fig. 6A and B). The heart slices of isoproterenol-induced rats (Group III) showed significant change in color. The infarcted region of heart tissue is clearly visible as a bright spot (white) and indicates the absence of lactate dehydrogenase (Fig. 6C). Pretreatment with (−) epicatechin (20 mg/kg body weight) (Group IV) showed significant reduction in infarct size in isoproterenol-induced myocardial infarcted rats (Fig. 6D). A major portion of the heart tissue stained positively with 2,3,5-triphenyl tetrazolium chloride and revealed greatly reduced infarct size (Group IV), compared to the heart slices of rats induced with isoproterenol alone (Group III).

4. Discussion

In this laboratory, the dose dependent effects of (−) epicatechin and the preventive effects of (−) epicatechin on creatine kinase-MB, electrocardiogram, cardiac troponin—I, lactate dehydrogenase-isoenzymes, oxidative stress, histopathology of myocardium (Stanely Mainzen Prince, 2011), membrane bound adenosine triphosphatases and minerals (Stanely Mainzen Prince, 2012) and cardiac mitochondrial damage (Stanely Mainzen Prince, 2013) in isoproterenol-induced myocardial infarction in Wistar rats were reported earlier. Based on the above proven preventive effects of (−) epicatechin on isoproterenol-induced myocardial infarction model, it has been proposed that pretreatment with (−) epicatechin might have the potential to act against lysosomal enzyme leakage involved in myocardial infarction. The present data

Fig. 5. Levels of thiobarbituric acid reactive substances in the lysosomal fraction of the heart tissue. Each column is mean ± standard deviation for eight rats in each group; NS as compared to normal control; *P < 0.05 as compared to normal control; †P < 0.05 as compared to ISO control (Duncan’s multiple range test); $—$ not significant, EC: (−) epicatechin, ISO: isoproterenol.

Fig. 6. (A)–(D) Images of 2,3,5-triphenyl tetrazolium chloride stained rat heart slices. (A) 2,3,5-Triphenyl tetrazolium chloride stained heart slice of normal control rat with completely viable tissue without any infarction. (B) 2,3,5-Triphenyl tetrazolium chloride stained heart slice of (−) epicatechin (20 mg/kg) treated group rats with completely viable tissue without any infarction. (C) 2,3,5-Triphenyl tetrazolium chloride stained heart slice of ISO (100 mg/kg) induced myocardial infarcted rat revealing infarcted regions. (D) 2,3,5-Triphenyl tetrazolium chloride stained heart slice of ISO (100 mg/kg) induced myocardial infarcted rat revealing infarcted regions. (D) 2,3,5-Triphenyl tetrazolium chloride stained heart slice of rat pretreated with (−) epicatechin (20 mg/kg) and then induced with myocardial infarction by ISO (100 mg/kg) showing much reduced infarction.

Fig. 7. Quantification of myocardial infarct size by cumulative planimetry. Each column is mean ± standard deviation for eight rats in each group; Normal control and EC treated group did not show any infarct region. *P < 0.05 as compared to ISO control (Duncan’s multiple range test); EC: (−) epicatechin; ISO: isoproterenol.

Fig. 7 clearly reveals the percentage myocardial infarct size quantified by the cumulative planimetry method. Normal control (Group I) and (−) epicatechin treated rat’s heart (Group II) did not show any infarct region. The isoproterenol induced myocardial infarcted rat’s heart (Group III) showed an increased percentage infarct region in planimetry analysis while pretreatment with (−) epicatechin (20 mg/kg) significantly (P < 0.05) reduced percentage infarct region in the isoproterenol-induced myocardial infarcted rat’s heart (Group IV).

Fig. 8 shows the percentage in vitro scavenging effects of (−) epicatechin on 2,2’-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) radical (total antioxidant activity). (−) Epicatechin scavened this radical in vitro in a concentration dependent manner (15, 30, 45, and 60 μM). The percentage scavenging activity of (−) epicatechin increased with increasing concentration. The scavenging of 2,2’-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) radical at various concentrations of (−) epicatechin, 15, 30, 45 and 60 μM were found to be 20.2%, 41.1%, 59.8% and 80.2%, respectively. (−) Epicatechin at the concentration of 60 μM revealed the highest percentage 2,2’-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) radical scavenging activity (80.2%). Thus, (−) epicatechin is a potent antioxidant.

(−) Epicatechin (20 mg/kg body weight) treatment to normal rats (Group II) did not show any significant effects on all the biochemical parameters studied. In this study, Group I is compared with Group II, Group III is compared with Group I and Group IV is compared with Group III.
revealed that increased levels of lysosomal lipid peroxidation, increased activities of lysosomal glycohydrolases, cathepsins and increased myocardial infarct size associated with myocardial infarction was lessened by (−) epicatechin and reduced myocardial damage in isoproterenol-induced myocardial infarcted rats. The activities of serum and myocardial β-glucuronidase, β-N-acetyl glucosaminidase, β-galactosidase, cathepsin-B and cathepsin-D were increased in isoproterenol-induced myocardial infarcted rats (Mayanskaya et al., 2000). The membrane deterioration of lysosomes by isoproterenol-induced lipid peroxidation resulted in the leakage of these enzymes from the enclosed sacs. (−) Epicatechin pretreatment decreased the activities of lysosomal enzymes both in the serum and myocardium by its inhibitory effect on lysosomal lipid peroxidation, thereby reducing the extent of lysosomal damage induced by isoproterenol.

Cathepsins are lysosomal proteases. Cathepsin-D is a lysosomal protease present in all animal cells. The release of β-glucuronidase enzyme is an index of lysosomal membrane integrity (Ravichandran et al., 1990). The decreased activities of β-glucuronidase and cathepsin-D observed in the heart lysosomal fraction in isoproterenol-induced myocardial infarcted rats resulted in decreased stability of lysosomal membrane. The elevated activity of β-glucuronidase and cathepsin-D in the cytosolic fraction is due to release of these enzymes from the lysosomes to cytosol in isoproterenol-induced myocardial infarcted rats. (−) Epicatechin pretreatment enhanced the activities of these enzymes in the lysosomal fraction and restricted the release of these enzymes from lysosomes to the cytosol, maintained membrane integrity and stabilized the lysosomal membranes.

Previously, the preventive effect of (−) epicatechin only on thiobarbituric acid reactive substances in the total heart homogenate was reported (Stanely Mainzen Prince, 2011). To the best of my knowledge, this is the first study performed on the levels of thiobarbituric acid reactive substances in the heart lysosomal fraction in myocardial infarcted rats. The increased levels of thiobarbituric acid reactive substances observed in the lysosomal fraction are due to the free radical mediated lysosomal membrane damage in isoproterenol-induced myocardial infarcted rats. These increased free radicals react with the lipid bilayer of intracellular organelles including lysosomes, which destabilizes lysosomal membranes and results in the rupture of lysosomes. Prior treatment with (−) epicatechin decreased the levels of lipid peroxidation products in the lysosomal fraction of the heart in isoproterenol-induced myocardial infarcted rats. Thus, (−) epicatechin decreased the excessive free radicals produced in the lysosomal membrane by isoproterenol and stabilized the lysosomal membrane. This effect revealed the antilipid peroxidation and membrane stabilizing properties of (−) epicatechin.

The leakage of cardiac troponin-I from the heart into the circulation is a consequence of isoproterenol-induced cardiac damage. Prior treatment with an antioxidant, (−) epicatechin lessened the levels of cardiac troponin-I in the serum of isoproterenol-induced myocardial infarcted rats.

Left ventricular dysfunction is predictable according to myocardial infarct size. Baks et al. (2005) reported a direct relationship between the extent of myocardial infarct size and mortality, since the myocardium does not have the ability to regenerate during infarction. Hence, it is of interest to examine the effect of (−) epicatechin on myocardial infarct size. In my study, the 2,3,5-triphenyl tetrazolium chloride staining test is followed to know the size of myocardial infarct and planimetry is used to quantify the infarct size. The white crystalline powder of 2,3,5-triphenyl tetrazolium chloride that forms a colorless solution in water is enzymatically reduced to brick-red precipitate of 1,3,5-triphenyl formazan dye in viable tissues with lactate dehydrogenase enzyme. In this study, normal control rats and normal rats treated with (−) epicatechin had no infarct regions in their heart. But a significantly increased infarct size and an absence of normal red color are observed in isoproterenol-induced myocardial infarcted rat's heart. This study revealed that oral pretreatment with (−) epicatechin significantly reduced the infarct size; thereby decreasing the extent of myocardial damage in isoproterenol-induced myocardial infarcted rats. These results confirmed the myocardial infarct reducing ability of (−) epicatechin.

In this study, (−) epicatechin scavenged 2,2′-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) radical (total antioxidant activity) concentration dependently. Thus, (−) epicatechin is a potent antioxidant. Isoproterenol metabolism produces increased lipid peroxidation. Thus, an antioxidant, (−) epicatechin inhibits lysosomal lipid peroxidation, prevents lysosomal enzyme leakage and reduces myocardial damage in isoproterenol-induced myocardial infarcted rats.

5. Conclusions and future directions

The present study revealed that (−) epicatechin reduced myocardial damage and alleviated isoproterenol-induced lysosomal enzyme leakage as demonstrated by preserving the integrity of lysosomal membranes by lessening lysosomal lipid peroxidation levels, maintaining lysosomal glycohydrolases and cathepsin activities, by virtue of its membrane stabilizing property. Understanding the mechanisms involved in the lysosomal enzyme leakage may prove beneficial in the prevention of myocardial infarction. Thus, lysosomal stabilization treatment may be effective in the prevention of myocardial infarction. This study as well as the previously reported studies on (−) epicatechin further strengthened the preventive effects of (−) epicatechin. Future studies of these findings should be performed in ischemia reperfusion injury animal model.

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References


