

# Protective Effect Of Ethanol Extract Of *Dodonaea Viscosa* Leaves Against Isoproterenol-Induced Myocardial Infarction

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## ABSTRACT

Myocardial infarction (MI), a life-threatening disorder, arises from the imbalance between oxygen supply and myocardial demand. Several plant products are known to exhibit creditable medicinal properties for the treatment of heart ailments instead of allopathic medicine which causes severe adverse effects. The aim of the present study was to investigate the protective effects of *Dodonaea viscosa* leaves against isoproterenol-induced myocardial ischemia. Wistar strain rats were pretreated with *Dodonaea viscosa* leaves (500mg/kg body weight) for 20 days and then intoxicated with isoproterenol (ISO) (20mg/100g, i.p. for 2 consecutive days). Cardioprotection was assessed by estimating plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and total protein. Troponin T was estimated in serum, the levels of malondialdehyde (MDA), reduced glutathione (GSH) were analyzed in plasma. In ISO-treated group, augmentation of cardiac markers in plasma and elevated lipid peroxidation were accompanied by decreased content of reduced glutathione in plasma. The prior administration of *Dodonaea viscosa* significantly prevented the isoproterenol-induced alterations and restored the cardiac markers. These findings proved the cardioprotective activity of *Dodonaea viscosa* during isoproterenol-induced myocardial ischemia. The protective activity of *Dodonaea viscosa* due to the phytochemical present in the leaves.

**Key words:** *Dodonaea viscosa*, Cardiac markers, Lipid peroxidation, Isoproterenol, Myocardial ischemia.

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## INTRODUCTION

Myocardial infarction is a clinical syndrome and remains the major cause of morbidity and mortality in all developed medicine is increasingly gaining greater acceptance from the public and medicinal profession. Myocardial infarction (MI) is an irreversible necrosis of tissue of a region of the myocardium caused by ischemia, which is a perfusion imbalance between demand and supply of blood to the heart via the coronary circulation (Li et al., 2016). Isoproterenol (ISO) administration in experimental animals provided a rapid, simple, and non-invasive method to generate myocardial damage status similar to that seen in humans with acute MI. In addition, ISO produced a model that had low mortality, high reproducibility, and validity compared with other animal models, which make it more appropriate for the assessment of potential cardioprotective agents (Wong et al., 2017). The main mechanism involved in isoproterenol-induction of myocardial ischemia is the generation of free radicals, reactive oxygen species, lipid peroxidation, oxidative stress, and calcium overload, which lead to the alteration in membrane permeability, causing apoptosis and necrosis and finally slowing the conduction between myocardial cells, triggering alterations in heart electrical activity (Kocak et al., 2016). Several plant products are known to exhibit creditable medicinal properties for the treatment of heart ailments instead of allopathic medicine which causes severe adverse effects (Iqbal et al., 2021).

Recent research has shown that medicinal plants with antioxidant properties are also able to impart cardioprotection. World Health Organization (WHO) estimates that 80% of total world's population presently uses medicines of herbal origin for primary health care. Hence, WHO has recommended the use of herbal medicines as an alternative medicine, especially in developing countries for various ailments. Plants constitute an important source of active natural products which differ widely in terms of structure and biological properties. They have a

remarkable role in the traditional medicine in different countries (Dianita et al., 2015). In recent years, 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, anthocyanins and other phenolic compounds (Mohamed et al., 2021). In order to evaluate the protective activity of *Dodonaea viscosa* on isoproterenol induced Myocardial infarction in rats.

## MATERIALS AND METHODS

### Animals

Male albino rats of Wistar strain approximately weighing 100-125g were used in this study. They were healthy animals purchased from the Indian Institute of Science, Bangalore. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (Temperature  $27 \pm 2^\circ$  C and 12 hour light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet and water were provided *ad libitum*. They were acclimatized to the environment for one week prior to experimental use. The animal feed composition is crude protein (22.3%), crude oil (4.01%), crude fibre (4.02%), Ash (8.02%) and sand silical (1.02%).

### Chemicals

Isoproterenol, Thiobarbituric acid (TBA), 2,4, Dinitrophenylhydrazine (DTNPH) and Reduced glutathione were purchased for sigma chemical company, Mumbai All other chemicals and reagents used in this study was of analytical grade with high purity and were obtained from Glaxo laboratories and Sisco Research laboratories, Mumbai, India.

### Plant material and preparation of extract

The leaf of *Dodonaea viscosa* was collected from Tamil University, Thanjavur. The collected leaves were cut into small pieces and shade dried at room temperature. The leaves were soaked with ethanol (50%) for 48 hours. A semi solid extract was obtained after complete elimination of alcohol under reduced pressure. The extract was stored in refrigerator until used. The extract contained both polar and non-polar phytochemicals of the plant material used. The leaves extract was dissolved in distilled water just before oral administration.

### Experimental design

Body weights of animals were recorded and they were divided into three groups of six animals each as follows. Group I : Normal animals received with standard fed and water to allow *ad libitum*. Group II: Administered isoproterenol (20mg /100g b.wt) suspended in 0.1ml of 0.9% saline subcutaneously twice at an interval of 24 hrs. Group III: Rat was pretreated with leaf of *Dodonaea viscosa* (500mg/kg b.wt) for a period of 20 days and Isoproterenol (20mg/100g subcutaneously twice at an interval of 24 hrs at the end of the treatment period. After the completion of experimental regimen, the rats were fasted overnight and blood samples collected by the puncturing the retro orbital plexus under light either an anesthesia.

### Collection of blood and preparation of plasma sample

At the end of the experimental period, the animals were anaesthetized using chloroform vapour prior to dissection. Blood was collected by cardiac puncture into EDTA containing tubes. The blood was allowed to standing at room temperature for 30 minutes and then refrigerated for another 30 minute. The resultant clear part was centrifuged at 3000rpm for 10minutes, and then the plasma was isolated and stored at refrigerated until required for analysis.

### Biochemical analysis

Protein was estimated by the method of Lowry *et al.* (1951). Reduced glutathione was estimated by method of Moron *et al.* (1979). Malondialdehyde was estimated by the thiobarbituric acid assay method of Beuge and Aust (1978). The serum GOT and GPT were estimated by the method of Reitman and Frankel (1957). Serum Cholesterol was estimated by Allain *et al.* (1974). Troponin- T estimated by the method of Bhaskar and Rao (2002). Serum triglyceride was determined by the method of Werner *et al.* (1981). The activity of serum lactate dehydrogenase was measured by the method of King (1965). Serum Creatine Phospho Kinase estimated by the method of Ochei and Kolhatkar (2000).

## RESULTS AND DISCUSSION

Myocardial infarction (MI) is caused due to an interruption in blood supply to any part of heart, resulting in death of cardiac tissue (Myocardial necrosis; MN). Consequences of MI include hyperlipidemia, peroxidation of membrane lipids and loss of plasma membrane integrity (Krushna et al., 2009). Cardiovascular diseases (CVDs) have a high prevalence in developing and developed countries and MI accounts for majority of deaths and disabilities (Agarwal et al., 2006). Isoproterenol (ISO) is a  $\beta$ -adrenergic agonist that causes severe stress in myocardium resulting in the infarct like necrosis of heart muscle (Welexer, 1978). Some of the mechanisms proposed to explain IP induced damage in cardiac myocytes include hypoxia due to myocardial hyperactivity, coronary hypotension, calcium overload, depletion of energy reserves and excessive production of free radicals due to oxidative metabolism of catecholamines (Mohanty et al., 2004). ISO induced MN in rats is a widely used experimental model evaluation of cardioprotective effect of various herbal drugs (Naik and Panda, 2008; Nandave et al., 2009), because pathophysiological changes following ISO administration in rats are comparable to those taking place during MI in humans (Nirmala and Puvanakrishnan, 1996).

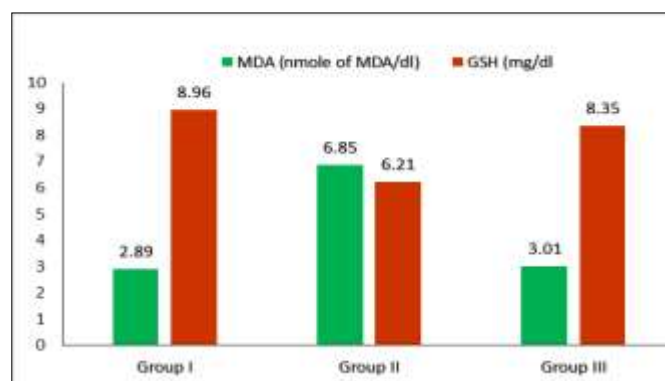
The present study was carried out to evaluate the “cardiac protective activity of *Dodonaea viscosa* on isoproterenol induced oxidative stress in rats” The observations made on different groups of experimental and control animals were compared as follows. Table I and figure I represents the levels of MDA and GSH in serum of normal and experimental rats. Group II isoproterenol induced oxidative stress rats showed a significant increased in the level of MDA when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the level of MDA when compared to group II. Group II isoproterenol induced oxidative stress rats showed a significant decreased in the level of GSH when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly increased in the level of GSH as compared to group II.

**Table I Effect of *Dodonaea viscosa* on MDA and GSH in experimental rats**

Parameters	Group I	Group II	Group II
MDA (nmole of MDA/dl)	2.89 ± 0.21	6.85 ± 0.30*	3.01 ± 0.28**
GSH (mg/dl)	8.96 ± 0.54	6.21 ± 0.15*	8.35 ± 0.48**

Values were expressed as mean ± SD for six rats in each group.

\* Significantly different from Group I, \*\* Significantly different from Group II



**Figure I Effect of *Dodonaea viscosa* on MDA and GSH in experimental rats**

Lipid peroxidation, a type of oxidative deterioration of polyunsaturated fatty acids has been linked with altered membrane structure and enzyme inactivation. Increased lipid peroxidation products in isoproterenol induced cardiotoxic rats appear to be the initial stage to the tissue making it more susceptible to oxidative damage. Increased free radical production may be responsible for the observed membrane damage as evidenced by the elevated lipid peroxidation

in terms of thiobarbituric acid reactive substances and lipid hydroperoxides (Devasagayam, 2001). *Dodonaea viscosa* (DV) pretreatment decreased the levels of lipid peroxides in the plasma of isoproterenol induced cardiotoxic rats. This shows the antilipoperoxidative effect of *Dodonaea viscosa*.

Oxygen free radicals are generated partially in the early stage of myocardial infarction and glutathione is involved in the reduction of hydrogen peroxide radicals, resulting in a decrease in glutathione levels during that period (Kocak et al., 1992). Glutathione is important in protecting the myocardium against oxygen free radical injury and thus a reduction in cellular glutathione content could impair recovery after short period of ischemia. The enhanced protective mechanism towards oxidative stress in myocardial infarction may consume reduced glutathione and depress reduced glutathione levels. The observed decrease in reduced glutathione levels might be due to increased utilization in protecting thiol containing proteins from lipid peroxides and from other reactive oxygen species. Pretreatment with *Dodonaea viscosa* increased the levels of reduced glutathione in the plasma of isoproterenol induced cardiotoxic rats. This shows the antioxidant property of *Dodonaea viscosa*.

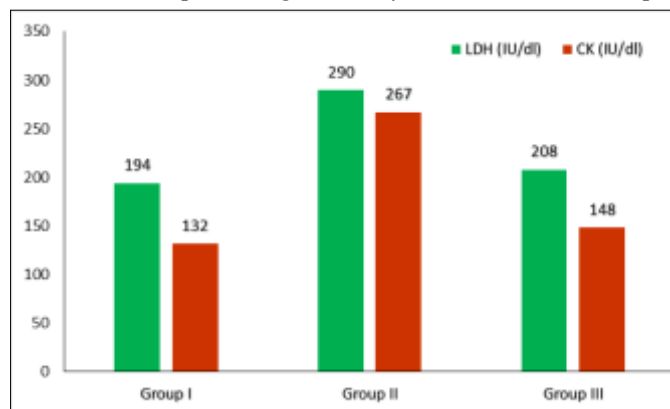
Table II and Figure II represents the activity of LDH and CK in serum of normal and experimental rats. Group II isoproterenol induced oxidative stress rats showed a significant increased in the activity of LDH when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the activity of LDH when compared to group II. Group II isoproterenol induced oxidative stress rats showed a significant increased in the activity of CK when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the activity of CK as compared to group II.

**Table II Effect of *Dodonaea viscosa* on LDH and CK activities in experimental rats**

Parameters	Group I	Group II	Group II
LDH (IU/dl)	194 ± 16.32	290 ± 29.32*	208 ± 18.65**
CK (IU/dl)	132 ± 11.24	267 ± 21.56*	148 ± 13.54**

Values were expressed as mean ± SD for six rats in each group.

\* Significantly different from Group I, \*\* Significantly different from Group II



**Figure II Effect of *Dodonaea viscosa* on LDH and CK activities in experimental rats**

Table III and Figure III represents the activity of SGOT and SGPT in serum of normal and experimental rats. Group II isoproterenol induced oxidative stress rats showed a significant increased in the activity of SGOT when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the activity of SGOT when compared to group II. Group II isoproterenol induced oxidative stress rats showed a significant increased in the activity of SGPT when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the activity of SGPT as compared to group II.

Table III Effect of *Dodonaea viscosa* on SGOT and SGPT activities in experimental rats

Parameters	Group I	Group II	Group II
SGOT (IU/dl)	52 ± 5.36	98 ± 8.59*	60 ± 6.78**
SGPT (IU/dl)	28 ± 3.47	68 ± 5.65*	32 ± 4.56**

Values were expressed as mean ± SD for six rats in each group.

\* Significantly different from Group I, \*\* Significantly different from Group II

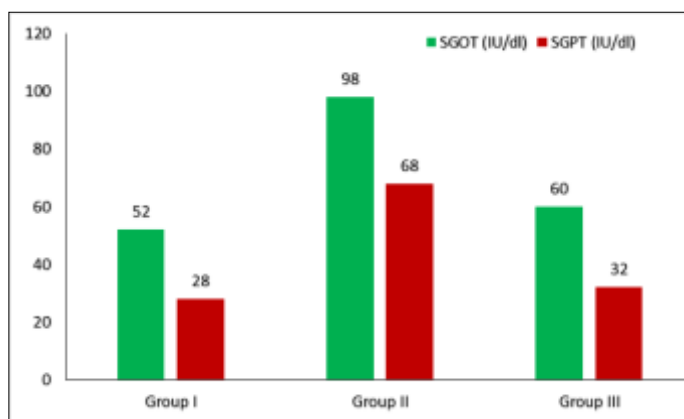


Figure III Effect of *Dodonaea viscosa* on SGOT and SGPT activities in experimental rats

Table IV and figure IV represents the levels of protein and troponin T in serum of normal and experimental rats. Group II isoproterenol induced oxidative stress rats showed a significant decreased in the level of protein and troponin T when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly increased in the level of protein and troponin T when compared to group II.

Table IV Effect of *Dodonaea viscosa* on protein in experimental rats

Parameters	Group I	Group II	Group II
Protein (gm/dl)	5.32 ± 1.04	8.95 ± 1.45*	6.21 ± 1.15**
Toponin T (µg/dl)	6.12 ± 1.20	12.35 ± 3.5*	7.65 ± 1.65**

Values were expressed as mean ± SD for six rats in each group.

\* Significantly different from Group I, \*\* Significantly different from Group II

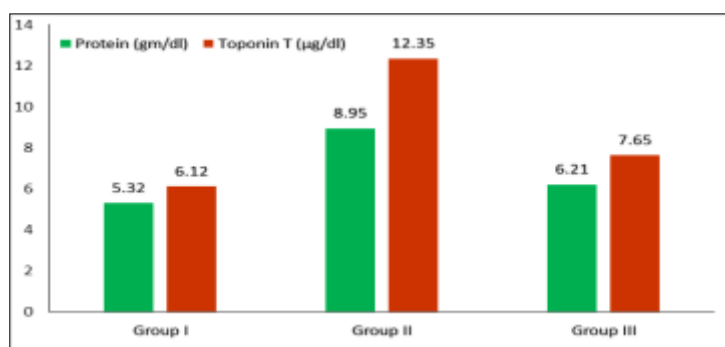


Figure IV Effect of *Dodonaea viscosa* on protein in experimental rats

The diagnosis of MI is based on clinical symptoms, electrocardiographic changes and characteristic pattern of changes in some serum and heart enzymes such as Creatine kinase (CK), Lactate dehydrogenase (LDH), Transaminases (SGOT, SGPT) and cardiac specific proteins like Troponins (Nigam, 2007). Cardiac markers or cardiac enzymes are protein from cardiac tissue found in the blood. The diagnosis of organ disease is aided by measurement of a number of non-functional plasma enzymes characteristics of that tissue or organ. The amount of enzymes released depends on the degrees or cellular damage, the intracellular concentration of the enzyme and the mass of affected tissue. The cause of the damage the enzyme released reflects the severity of the damage (Vaudha et al., 2006).

In this study, significant decline was shown in the activities of cardiac markers such as SGOT, SGPT, LDH and CK in the heart of acute ISO-treated rats, which is consistent with earlier reports (Plebani 2001; Nigam, 2007). Decreased activities of these enzymes were due to the leakage from the damaged heart tissues into the blood stream as a result of necrosis induced by isoproterenol in rats. Wexler et al. (1978) observed that these cardio-specific marker enzymes are released from the heart into the blood during myocardial damage due to myofibril degeneration and myocyte necrosis. Significant increase was noticed in the activities of cardiac markers (SGOT, SGPT, LDH and CK) in serum of acute ISO-treated rats, which is consistent with earlier reports (Plebani 2001), might be due to enhanced susceptibility of myocardial cell membrane to the isoproterenol mediated peroxidative damage, resulting in increased release of these diagnostic marker enzymes into the systemic circulation.

In the present study, the prior administration of *Dodonaea viscosa* was significantly prevented the isoproterenol-induced elevation in the levels of diagnostic marker enzymes in serum, indicating the cytoprotective activity of *Dodonaea viscosa*. Thus, it is possible that likewise *Dodonaea viscosa* may also prolong the viability of myocardial cell membrane stabilizing action.

A serum marker that once held promise as cardiac specific marker for MI is the cardiac troponin. Troponin is a protein found in cardiac tissue and located in the thin filament of striated muscles consisting of the three subunits Troponin T, Troponin I and Troponin C. Of the three troponins T and I are being used as the biochemical markers for the diagnosis myocardial injury. When the myocardial damage occurs the cytosolic troponins reach the blood stream quickly resulting in a rapid peak of serum troponin observed during the first few hours. This is followed by the release of structurally bound troponin resulting in a second peak lasting for several days (Nigam, 2007). In this study, significant increased level of Troponin T and total protein in serum of ISO-treated rats. Increased level of troponin T and total protein were due to the leakage from the damaged heart tissues into the blood stream as a result of necrosis induced by isoproterenol in rats. Pretreatment with *Dodonaea viscosa* to ISO-treated rats restored the level of troponin T in serum, indicates the membrane stabilizing action of *Dodonaea viscosa*.

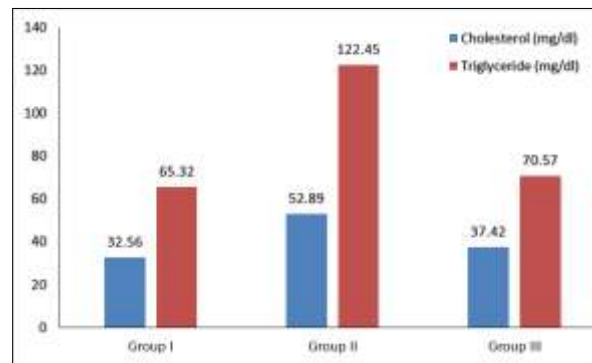
Table V and Figure V represents the levels of cholesterol and triglyceride in serum of normal and experimental rats. Group II isoproterenol induced oxidative stress rats showed a significant increase in the level of cholesterol when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the level of cholesterol when compared to group II. Group II isoproterenol induced oxidative stress rats showed a significant increase in the level of triglyceride when compared to Group I rats. Group III isoproterenol induced oxidative stress rats treated with *Dodonaea viscosa* significantly decreased in the level of triglyceride as compared to group II.

**Table V Effect of *Dodonaea viscosa* on cholesterol and triglyceride in experimental rats**

Parameters	Group I	Group II	Group II
Cholesterol (mg/dl)	32.56 ± 2.34	52.89 ± 4.68*	37.42 ± 3.04**
Triglyceride (mg/dl)	65.32 ± 3.58	122.45 ± 8.65*	70.57 ± 4.21**

Values were expressed as mean ± SD for six rats in each group.

\* Significantly different from Group I, \*\* Significantly different from Group II



**Figure V Effect of *Dodonaea viscosa* on cholesterol and triglyceride in experimental rats**

ISO-treated rats showed increased levels of plasma total cholesterol and TG. Our results are in agreement with previous report (Manjula et al., 1992). Hypercholesterolemia and hypertriglyceridemia were seen in ISO-treated rats which might be due to increased mobilization of lipids from adipose tissue (Stralfors et al., 1984). DV decreased the levels of plasma total cholesterol and TG. High consumption of plant has been reported to contribute to the decreased serum cholesterol and TG in rats (Senthil et al., 2007). Hypocholesterolemic effect of DV may be mediated via reduction in the HMG-Co A reductase activity (Lee et al., 199).

Lipid metabolism plays an important role in myocardial necrosis produced by ischemia (Mathew et al., 1981). An ISO-treated rat showing altered lipid profiles in the heart agrees well with a previous report (Senthil et al., 2007). The significant increase observed in the lipid profiles except phospholipids in the rat treated with ISO alone could be due to enhanced lipid biosynthesis by cardiac cyclic adenosine monophosphate (cAMP) (Paritha and Devi, 1997). A significant rise in cholesterol content suggested that the redistribution of cholesterol in ischemic cells (Venter et al., 1991). The elevated level of cholesterol in heart is well associated with myocardial ischemia (Rouslin et al., 1982). In aerobic conditions, cardiomyocytes prefer free fatty acids for energy. Ischemic myocardium is not in a position to oxidize the available fatty acids and results in the accumulation of fatty acyl coA derivatives (Whitmer et al., 1978). In this study, *Dodonaea viscosa* treatment was shown to attenuate the alterations of myocardial lipids. This may be due to its hypolipidemic effect on cardiomyocytes.

## CONCLUSION

Several plant products are known to exhibit creditable medicinal properties for the treatment of heart ailments and need to be explored to identify their potential application in prevention and therapy of human ailments. Keeping in view the wide use of *Dodonaea viscosa* evaluated in the cardio protective activity. Pretreatment with *Dodonaea viscosa* on isoproterenol-induced rat exerts the following results. Reduce the oxidative stress by decreased lipid peroxidation and increased glutathione (GSH). Normalized the cardiac marker enzymes such as SGOT, SGPT, LDH and CK and cardiac specific protein Troponin T and total protein Restore the lipid profile. *Dodonaea viscosa* pretreatment proved to be effective in reducing the extent of myocardial damage, associated lipid peroxidation, thus maintaining, as suggested by biochemical indices, the structure and function of the myocardium. The potential cardio protective activity of *Dodonaea viscosa* due to the presence of therapeutic phytochemicals such as flavonoids, terpenoids, steroids and tannin were reported.

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