EFFECT OF HYDRO - ALCOHOLIC EXTRACT OF *Apium graveolens* Linn ON ISOPRENALINE INDUCED MYOCARDIAL INFARCTION IN ALBINO RATS.

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ABSTRACT: Myocardial infarction is a medical emergency what demands both immediate medical and action of emergency medical services. Several plant products have been known to exhibit curable medical properties and have been used for prevention and therapy of heart ailments. Notable among them are the seeds of *Apium graveolens*. Hence the present experiment was undertaken to study the effect hydroalcoholic extract of *Apium graveolens* on isoprenaline induced myocardial infarction in albino rats. The experiment was conducted for 21 days and the mode of action of drug on the marker enzymes LDH, CPK, GOT was studied. The effect of drug on the lipid profile of liver enzymes was also studied. Hydroalcoholic extract of *Apium graveolens* showed cholesterol reduction. The level of cardiac marker enzymes LDH, CPK &GOT also showed reduction activity due to 21 days of treatment by the hydroalcoholic extract of *Apium graveolens*.

KEYWORDS: - *Apium graveolens*, Cardioprotective, Isoprenaline, Myocardial infarction

1. INTRODUCTION

Myocardial infarction simply means the irreversible necrosis of heart muscle and the myocardium. The deposition of fat including cholesterol, on the inner lining of arteries, make it hard and narrow, resulting in reduced blood supply to the visceral organs. It gradually prevents blood flow and results in a block in the artery. This condition is called arteriosclerosis and when it involves coronary vessels, myocardial infarction can occur.

WHO estimated that myocardial infarction is a medical emergency and the leading cause of death for both men and women all over the world. In India cardiovascular disease (CVD) is the leading cause of death. The death due to CVD in India was 32% of all death in 2007 and is expected to rise to 2.03 million in 2012.

The risk factors for myocardial infarction are old age, tobacco smoking, hyper-cholesterolemia , hyperhomocystinemia, diabetes, high blood pressure, obesity etc. Many of these risk factors are modifiable; so many heart attacks can be prevented by maintaining a healthier life style. To keep the heart healthy, we have tried to use many medical systems. Among them, first is the Ayurveda, which offers a detailed account of heart diseases, factors leading to heart attack, better life and precautions. Modern medicines play an important role in treating this medical emergency.

Isoprenaline, one of the most active sympathomimetic amines, acts almost exclusively on β – receptors, there by affecting the heart, the smooth muscles of the bronchi, skeletal muscles, vasculature and the muscles of the alimentary tract. It stimulates heart by the action of β1 and β2 receptors, which increases circulation by increasing cardiac output producing dialation in arteriolar blood. This further increases myocardial lactate production, which is an induction of greater cardiac hypoxia. Cardiac arrhythmia may occur readily by large or repeated doses of isoprenaline in animals, which may lead to myocardial necrosis or to cardiac arrest. When the heart is subjected to an increased workload, it causes myocardial infarction and there is an increase in the level of lipid peroxides in the myocardium causing membrane damage and dysfunction (1).

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Nature has been a source of medicinal agents for thousands of years and an impressive number as modern drugs have been isolated from natural resources, based on their uses in traditional medicine. A number of medicinal plants are in use in the treatment of various ailments of heart. Hence these medicinal plants have been crucial in sustaining the health and well being of mankind. *Apium graveolens* or celery is one of the medicinal plants from Apiaceae family, said to be useful in cardiac treatment. Hence, this legendary folk medicine has been used to screen its cardioprotective activity in isoprenaline induced cardiac damage in rodents.

2. MATERIALS AND METHODS

2.1. Extraction

Hydroalcohol extract was prepared as follows:

250gm of dried Celery seed was digested for 24hrs.with 2.5 litre of 50% ethanol by refluxing. The mixture was filtered and alcohol was recovered from the extract. The remaining extract was concentrated to 250ml.10ml of the concentrated extract was evaporated in a tarred evaporating dish and dried to constant weight at 105^0C, cooled and weighed. The extracted drug matter was found to be 137mg/ml.

2.3. Animals

Adult albino rats of either sex weighing 100-200 gm were obtained and acclimatized for 5 days before experiment. They were fed with standard pellet diet and water ad libitium.

2.4. Cardio-protective Activity

Rats were randomly distributed into 4 groups with 6 each under identical conditions as follows.

Group I Normal rats (Distilled water only)

Group II Control rats (Distilled water for 15 days+Isoprenaline (8.5mg/100g) on the 16^{th} & 17^{th} day)

Group III Drug extract 250mg/kg for 15 days+ Isoprenaline(8.5mg/100g)On the 16^{th} & 17^{th} day.

Group IV Drug extract 500mg/kg for 15 days+ Isoprenaline(8.5mg/100g) on the 16^{th} & 17^{th} day.

Isoprenaline hydrochloride(ISO) was suspended in distilled water and administered subcutaneously to the rats at a dose of 8.5 mg/100g on two consecutive days to induce myocardial infarction.

Blood was collected by retro-orbital sinus puncture from all surviving rats after 48hrs of first injection. The collected blood was centrifuged at 3000 rpm, within one hour and the serum was analyzed for various biochemical parameters such as marker enzymes in semi auto-analyzer using diagnostic kits.

Results of the biochemical estimations were reported as mean ± standard deviation of 6 rats in each groups.

3. RESULTS AND DISCUSSION

The percentage of increase in the body weight of the untreated rats were 4.5%increase in the case of normal group, where as only isoprenaline treated group the body weight increase was 26.28%. On the other hand the body weight of the drug treated rats (Group III and Group IV) were increased by 33.4and 26.4 % respectively (Table I).

The levels of cardiac marker enzymes were evaluated using the test drug orally. A significant increase in the level of SGOT, LDH and CPK was observed in the Isoprenaline administered rats when compared to the normal rats. Pretreatment with the drug extract (celery seed) at both doses significantly decreased the level of SGOT, LDH, and CPK when compared with the isoprenaline treated rats. (Table 2)

Myocardial infarction is associated with the ischemic necrosis of cardiac muscle due to decrease in the supply of blood to a portion of myocardium below a critical level necessary for viability and proper phys

Table 1. Effect of hydro-alcoholic extract of *Apium graveolens* on body weight(gm)of isoprenaline induced myocardial infarction in albino rats

Group	Treatment	Initial weight Mean±S.D.	Final weight Mean±S.D.	Percentage of change
I	Normal (Distilled water)	113.3± 9.4	118.3 ± 11.4	4.5
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	126.7 ± 12.4	160 ± 19.1	26.3
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day	170 ± 16.3	226.7± 41.5	33.4
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day	151.7 ± 8.3	191.7 ± 5.7	26.4

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I. Values in group III and IV are compared with group II.

Table 2. Effect of hydro-alcoholic extract of *Apium graveolens* on the marker enzymes of isoprenaline induced myocardial infarction in albino rats.

Group	Treatment	SGOT(IU/L) Mean ± S.D.	LDH(IU/L) Mean ± S.D.	CPK(IU/L) Mean ± S.D.
I	Normal (Distilled water)	118 ± 14.4	97 ± 22.8	134 ± 7.2
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	*** 346 ± 65.1	** 212.6 ± 50.6	*** 392.3 ± 24.7
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 116.8 ± 11.7	*** 94 ± 6.3	** 160.8 ± 30.9
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 78.7 ± 11.4	*** 75.2 ± 12.4	*** 107.1 ± 21.77

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I; Values in group III and IV are compared with group II; ***P<0.01,**P<0.02,*P<0.05 (P Value denotes significance)

iological function. A disparity between the oxygen requirement of the myocardium and the ability of the coronary artery to meet it result in the ischemic necrosis of the heart muscle leading to the development of arteriosclerosis which also may be a cause of myocardial infarction.

Isoprenaline is a β-adrenergic receptor against which could stimulate the β-cells of the heart and induce myocardial infarction in albino rats, when given in high doses (2). Hence we chose isoprenaline in our study to induce myocardial infarction in the rats. By noting the biochemical changes in the animal model it is possible to gain more facts into the mechanism leading to the altered metabolic process in human myocardial infarction. The diagnostic markers in the myocardial infarction such as SGOT, CPK, LDH, SGPT, ALP, lipid profile, lipid peroxide,

Table 3. Effect of hydro-alcoholic extract of *Apium graveolens* on liver function test of the isoprenaline induced myocardial infarction in albino rats

Group	Treatment	SGPT (IU/L) Mean± S.D	ALP (IU/L) Mean± S.D	Serum Bilirubin (mg/dL) Mean± S.D	Total protein (gm/dl) Mean±S.D	Seram Albumin (gm/dl) Mean± S.D	Globulin (gm/dL) Mean± S.D
I	Normal (Distilled water)	41±2.6	138±5.3	0.6±0.1	5.4±0.4	3 ± 0.3	1.6±0.2
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	*** 121.5±1.6	161.8±3.1	0.2±0.1	5.7±0.7	3.3 ± 0.6	2.4 ±0.1
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 36.6±8.9	98.3±12.6	0.16±0.2	5.6±0.4	3.3 ± 0.4	2.3±0.1
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 31.5±8.8	84.5±10.8	0.25±0.1	5.6±0.9	3.2 ± 6	2.5±0.3

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I; Values in group III and IV are compared with group II; ***P<0.01,**P<0.02,*P<0.05 (P Value denotes significance)

Table 4. Effect of hydro alcoholic extract of *Apium graveolens* on the lipid profile of the isoprenaline induced myocardial infarction in albino rats

Group	Treatment	Triglyceride (mg/dl) Mean±S.D	Cholesterol (mg/dl) Mean±S.D	HDL cholesterol (mg/dl) Mean±S.D	LDL Cholesterol (mg/dl) Mean±S.D	LDL/HDL
I	Normal (Distilled water)	81 ± 6.2	88 ± 4.2	25 ± 1.2	39.1 ± 1.9	1.6
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	*** 112.6 ± 5.9	*** 125.5 ± 11.3	21.3 ± 3.0	*** 81.6 ± 9.7	3.8
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	82.6 ± 5.6	90 ± 7.0	24 ± 3.05	40.4±7.0	1.7
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	82.3 ± 9.0	*** 77.6 ± 6.7	21 ± 2.6	40.2 ± 6.5	1.9

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I; Values in group III and IV are compared with group II; ***P<0.01,**P<0.02,*P<0.05 (P Value denotes significance)

glutathione help in assessing the functional state of the heart and the body as a whole. Rats administered with isoprenaline showed elevation of the myocardial marker enzymes LDH, SGOT, CPK denoting the extent of heart damage due to isoprenaline. These enzymes are useful in assessing the severity and progress of the disease.

A significant increase was noted in the body weight of the drug treated rats (Table 1).which denotes a good intake of food for growth by rats, where as an insignificant weight gain was observed in the myocardial rats. This suggests the positive effects of the drug.

Table 5. Effect of hydro alcoholic extract of *Apium graveolens* on renal function & blood sugar of the isoprenaline induced myocardial infarction in albino rats

Group	Treatment	Urea(mg/dl) Mean ± S.D	Creatinine (mg/dl) Mean ± S.D	Glucose(mg/dl) Mean ± S.D
I	Normal (Distilled water)	38 ± 3.2	0.6 ± 0.1	95 ± 7.9
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	45.1 ± 7.9	1.5 ± 1.5	100 ± 7.5
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	37.3 ± 32.3	0.8 ± 0.12	104.6 ± 9.1
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	35 ± 3.05	0.6 ± 0.1	105.8 ± 13.7

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I; Values in group III and IV are compared with group II; ***P<0.01,**P<0.02,*P<0.05 (P Value denotes significance)

Table 6. Effect of hydro alcoholic extract of *Apium graveolens* on liver & heart lipidperoxides and glutathione of isoprenaline induced myocardial infarction in albino rats

Group	Treatment	Liver Lipid peroxides (mmoles/100g tissue) Mean ± S.D	Heart Lipid peroxides (mmoles/100g tissue) Mean ± S.D	Liver Glutathione(mg/100g tissue) Mean ± S.D	Heart Glutathione(mg/100g tissue) Mean ± S.D
I	Normal (Distilled water)	1.05 ± 0 .02	0.8 ± 0.1	98.7 ± 24.2	258.3 ± 29.5
II	Control rats (distilled water for 15days+ Isoprenaline(8.5mg/100g) on the 16th & 17th day)	*** 1.8 ± 0.05	*** 1.9 ± 0.08	99.4 ± 19.9	*** 120.7 ± 18.6
III	Drug extract 250mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 1.25 ± 0.04	*** 1.6 ± 0.06	*** 209.6 ± 27.1	*** 275.5 ± 26.4
IV	Drug extract 500mg/kg for 15days+Isoprenaline(8.5mg/100g) on the 16th&17th day)	*** 1.4 ± 0.03	*** 1.4 ± 0.07	*** 276.9 ± 17.3	*** 291.2 ± 32.8

Values are mean ± standard deviation(S.D) of 6 rats in each group; Values in group II are compared with group I; Values in group III and IV are compared with group II; ***P<0.01,**P<0.02,*P<0.05 (P Value denotes significance)

Results showed an alteration in the level of marker enzymes SGOT (serum glutamate oxaloacetate transaminase), CPK (Creatinine phosphokinase) and LDH (Lactate dehydrogenase) in myocardial infracted rats. The expression myocardial infarction refers to necrosis of a group of cardiac muscle as a result of ischemia causing leakage of the marker enzymes into the blood stream which was observed in our study. There was no significant increase in the serum GOT, CPK, and LDH values in rats administered with hydro alcoholic extract of *Apium graveolens* either at lower or higher dose levels when compared to the normal rats.

Our observations are in correlation with the study of Alhat et.al (3). They have reported that *Apium graveolens* traditionally used for heart palpitaions and liver disorders. A total of 34 volatile compounds were identified including 6 alco-

hols 9 terpenes and sesquiterpene hydrocarbons, 2 ketones, 7 phthahalides and 5 psoralens (4). These compounds may be responsible for the prevention of the increase of the marker enzymes released due to the necrosis of cardiac muscles.

We have also observed an increase in the level of triglyerides, total cholesterol and LDL cholesterol in myocardial infracted rats. Treatment with hydro alcoholic extract of *Apium graveolens* showed improvements in myocardial infarction by significantly suppressing the level of triglyceride, total cholesterol and LDL cholesterol. The result of table IV shows the effect of hypoglycemic enzymes like glucose-6-phosphate and HMG CoA reductase which is a rate limiting step in cholesterol biosynthesis, an unknown compound of the extract may interfere with the step. Tsi *et al* (5) have observed that the level of serum total cholesterol (TC), low density lipoprotein cholesterol (LDC-C) and triglycerides (TG) to be decreased in the heart of *Apium graveolens* treated rats which support our study.

Biochemical parameters like bilirubin, SGPT, ALP and protein gives an idea regarding the functional state of liver. As evidence in the Table III an increase in level of SGPT was observed in isoprenaline treated group of rats. Pretreatment with the drug decreased the level of SGPT significantly as reported by Sing and Hunda (1970). The level of total protein, albumin and globulin did not differ in experimental groups. *Apium graveolens* has been reported as a potent plant against experimentally induced hepato carcinogenesis in wistar rats (Sarwat Sulthana et.al; 2005).

Parameters like urea and creatinine gives an idea about the functional state of kidney. Increase in the level of urea and creatinine were seen in the isoprenaline treated group of rats. The test extract treatment was also found to influence kidney function significantly (Table V). However no significant difference in blood glucose was noted in *Apium graveolens* treated groups.

The results of Table IV shows an increase level of lipid peroxide in liver and heart tissue of the isopreanaline treated rats. This increase in the peroxides shows the oxidative damage of heart by isoprenaline. Myocardial ischemia have been found to be associated with massive loading in the mitochondria with calcium which interferes with mitochondrial function and produce cell injury, which leads to increased concentration of lipid peroxide as observed in our study. Decreased glutathione level may be due to its increased utilization in protecting SH groups containing proteins from the action of free radicals. Glutathione participates directly in the destruction of hydrogen peroxide and also promotes the formation of reduced form of ascorbate which has high antioxidant activity. As reported by Alhat *et al.,* pretreatment with methanolic extract of *Apium graveolens* 250mg/kg and 500mg/kg p.o significantly inhibited the decrease in myocardial reduced glutathione (GSH) and increase in lipid peroxidation. Thus pretreatment with *Apium graveolens* decreased lipidperoxide level and maintained glutathione content to near normal level. Glutathione and lipid peroxides are correlated always and the mechanism is not known.(Table VI)

The present findings using two doses of test drug showed significant usefulness in myocardial disease. Since the present study was only for a limited period, further evaluation on its antioxidant potential and mode of action could not be assessed. Hence, further studies are warranted to throw more light into the uesfulness of this potential herbal remedy in cardiac diseases in human beings.

4. CONCLUSION

The level of cardiac marker enzymes SGOT,CPK and LDH were increased in the ISO treated control group, where as the levels were significantly decreased in the drug treated rats.The levels of cholesterol and triglycerides were increased in the serum of Isoprenaline alone treated rats.A significant reduction in cholesterol level was observed in the *Apium graveolens* treated rats.The level of lipidperoxide in the liver and heart tissue were decreased in drug treated rats compared to the control rats.The level of glutathione in the liver and heart tissue were increased in drug

treated rats compared to the control rats.No significant changes in LFT and Kidney function tests were noticed .

Our observations in the present study suggests that the administration of the *Apium graveolens* may be beneficial in the treatment of myocardial infarction.However further study is required before exploring its usefulness in humanbeings.

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