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Original Research Article

# TO EVALUATE THE EFFECT OF NARINGENIN AGAINST MYOCARDIAL ISCHAEMIC REPERFUSION INJURY IN LANGENDORFF PERFUSION RAT HEART

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**ABSTRACT**

Cardiovascular Diseases are the major cause of human morbidity and mortality worldwide including india.it is reported that coroneryartey ischaemia/reperfusion injury is known to occur during restoration of coronary blood flow after a period of myocardial ischaemia and triggers myocardial cell injury and necrosis. In addition apoptosis, inflammation, oxidative damage play important role in I/R injury progression, therefore the modulation of apoptosis, inflammation and oxidative damage and of related cascade responses must be consideredas a therapeutic strategy for treating cardiovascular disease.

**Keywords:** Naringenin, ischaemia, rat heart, apoptosis

## INTRODUCTION

Brief periods of ischemia trigger a ‘‘self-defense’’ effect which protects myocardial tissue from following and more severe ischemic episodes.[1] This endogenous mechanism of cardioprotection, known as ischemic pre-conditioning (IPC), is a multifactorial phenomenon which requires the involvement of several elements. Presently, it is widely accepted that the activation of potassium flows across the inner mitochondrial membrane, through specific ion channels, confers on cardiomyocytes an increased resistance against the ischemia/reperfusion (I/R) injury. Consistently, the development of activators of mitochondrial potassium channels is considered an intriguing pharmacological strategy for anti-ischemic cardioprotection.[2–4] The mitochondrial ATP-sensitive potassium channel (mitoKATP) has been the first and most intensely investigated target for this purpose.[5,6] More recent experimental evidence indicates that also the large-conductance calcium-activated potassium channels (BK) are present in the inner mitochondrial membrane. Noteworthy, the protective effects of a number of exogenous BK-openers have been clearly demonstrated in different models of I/R injury.[7–10] The activation of mitochondrial potassium channels, and in particular of mitochondrial BK channels (mitoBK), protects myocardial cells through several pathways. Among them, the activation of mitoBK-mediated potassium currents leads to a partial mitochondrial membrane depolarization, with consequent reduction of the electrical driving force for calcium ions. This leads to reduce the up-take of calcium ions into the matrix during ischemia, and the cell death during reperfusion.[12] Naringenin is one of the principal flavonoids occurring in many fruits of the genus Citrus, such as grapefruit and orange, whose anti-ischemic effects have been described in experimental models of I/R

## MATERIALS AND METHODS

It is a crosscontrol experimental study of duration 4 weeks in the department of physiology, kgmulucknow with collaboration of pediatrics department 12 male wistar albino rats weighing 250-300 gramswere recruited for study after approval of the ethical committee. Naringenin is the drug used for study

## RESULTS

**Statistical Tools Employed:** Statistical analysis was applied to all data using SPSS Statistics for Windows,

Version 23 (IBM Corp., Armonk, NY, USA). The values were represented in Number (%) and Mean ± SD.

The following Statistical formulas were used:

1. **Mean:** To obtain the mean, the individual observations were first added together and then divided by the number of observation. The operation of adding together or summation is denoted by the sign

The individual observation is denoted by the sign X, number of observation denoted by n, and the mean by $\overline{X}$.

$$\overline{X} = \frac{\Sigma X}{\text{No. of observations (n)}}$$

2. **Standard Deviation:** It is denoted by the Greek letter □. If a sample is more than 30 then.

$$\sigma = \sqrt{\frac{\Sigma (X - \overline{X})^2}{n}}$$

When sample in less than 30 then.

$$\sigma = \sqrt{\frac{\Sigma (X - \overline{X})^2}{n-1}}$$

Student't' test: To test the significance of two means the student 't' test was used

$$t = \frac{\overline{X}_1 - \overline{X}_2}{S\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

$$\text{where } S2 = \frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2}{N_1 + N_2 - 2}$$

where, $\overline{X}_1$, $\overline{X}_2$ are means of group 1 and group 2

N1, N2 are number of observation group1 and group 2

SDI, SD2 are standard deviation in group1 and group 2

Level of significance: "p" is level of significance

p > 0.05 Not significant

p <0.05 Significant

p <0.01 Highly significant

p <0.001 Very highly significant

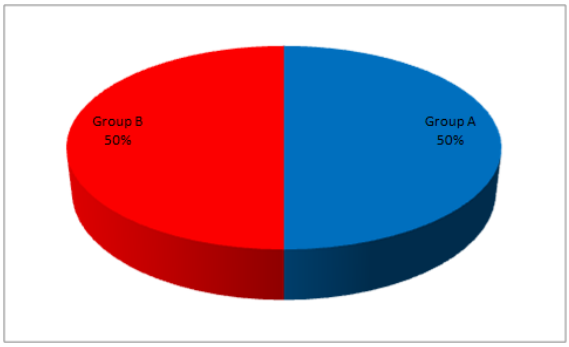
**Study Groups:** The male Wistar rats were divided into two groups as per following:

**Group I:** (n= 6) Control/ Placebo Group, Animals of this group received only standard rat feedsimilar to other animals for whole of studyperiod.

**Group II:** (n=6) Treated group, Animals of this groups received treatment of Naringenin (50mg/kg/day) orally for a duration of 4 weeks.

**Table 1: Group wise distribution of study population**

| Group | No. of Rats | Percentage |
|---|---|---|
| Group A | 06 | 50 % |
| Group B | 06 | 50 % |




**Study of Heart Rate (HR):** Heart rate (HR) was recorded weekly throughout the entire experimental procedure. The HR readings were obtained from NIBP machine (AD Instrument Australia), housed in Departmental facility, King George's University, Lucknow. Initially, between control (Group A) and Treated (Group B; Naringin treated group) there was no difference in the HR parameters. Initially, the HR was recorded to be 403±20.49 and 400.83±7.38 (p=0.40) for (placebo) control and (Naringenin) treated groups respectively.

**Table 2: Between Group Comparison of Heart Rate (HR) per min**

| Parameters | Group A (n=6) | | Group B (n=6) | | Statistical Significance |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | 'p' |
| HR (per min) (Before Week One) | 403 | 20.49 | 400.83 | 7.38 | 0.40 |
| HR (per min) (End of Week One) | 390.67 | 39.69 | 424.33 | 19.40 | 0.04* |
| HR (per min) (End of Week Two) | 404.33 | 21.23 | 411.67 | 30.60 | 0.32 |
| HR (per min) (End of Week Three) | 421 | 17.82 | 374.16 | 34.79 | 0.007** |
| HR (per min) (End of Week Four) | 415 | 20.07 | 375.5 | 19.40 | 0.003** |

**Study on Langendorff values (Perfusion Pressure, Perfusion Flow and Left ventricular developed pressure):** After administration of Naringenin for duration of 4 weeks in treatment group, all the (control and treated both) Rat hearts were isolated. The isolated rat hearts were perfused for 30 minute

stabilization period. Then hearts from both control and treated groups were subjected to global ischemia (reduced flow) 15min and reperfusion was subjected to 45 min. Later, Langendorff values (Perfusion Pressure, Perfusion Flow and LVPD) were continuously monitored with a computer-based data acquisition system (PowerLab/4S with Chart 5 software, AD Instruments, Gladstone, Australia. Left ventricular developed pressure (LVPD) was calculated using the following formula (LVDP = LVSP-LVEDP).

**Table 3: Between Group Comparison of Langendorff values End of Week Four**

| Parameters | Group A (n=6) | | Group B (n=6) | | Statistical Significance |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | 'p' |
| Perfusate pressure (mmHg) | 136 | 3.52 | 135.66 | 2.42 | 0.42 |
| Perfusate flow (ml/min) | 10 | 00 | 10 | 00 | -- |
| LVDP (mmHg) | 20.33 | 8.64 | 18.33 | 3.20 | 0.30 |

## DISCUSSION

ALL weekly analysis revealed that amongst all the indices, Naringenin lowers down the value of QRS (seconds) between Control and Naringenin treated animals (p=0.04). The final chart for ECG revealed that Naringenin lowers down QT (seconds) and overall heart rate with a p value of 0.014 and 0.008 respectively between Control and Treated groups.

On the other hand, Naringenin also lowered down the values of Langendorff at the end of week four (final). Perfusion pressure decreased from 136 to 135.66 whereas, LVPD (Left ventricular developed pressure) lowered down from 20.33 to 18.33 between control and treated animals. We found that the basis of protective nature of bio-active molecule Naringenin lies in its structure: It is now well known that Naringenin has anti-oxidative effects. Like all other flavonoids, Naringenin too has such a structure that allows scavenging of free radicals. The additional attribute with Naringenis is that it has ability to induce antioxidants in the system (116). Generally, the anti-oxidant activity of any molecules resides on the number of OH bonds that possesses. This value for Naringenin is 3, which is quite high when compared to other flavonoid. Other special feature of Naringenin is that its structure allows high value of resonance thus its structure is very stable in its native form. These factors make Naringenin a very suitable drug candidate in the context of CVD as the results suggested.

This study clearly has demonstrated the protective effect of Naringenin on ischemia-reperfusion induced rat heart. In a broader aspect Naringenin is found to be a potent drug candidate against cardiovascular diseases.

## CONCLUSION

Cardiovascular diseases (CVD) attributes to the maximum number of deaths in world. This problem is more severe in developing countries like India, due to lack of primary health care services. The prime reason for the mortality due to CVD is ischemic heart diseases. Plant and their products have been known to have therapeutic values since ancient times. Amongst all the bio-active compounds isolated from plants, Flavonoids are known to have maximum activity due to high radical scavenging potential. We used citrus derived Flavonoid, Naringenin for its effect on freshly isolated ischemic rat heart. The following observations were drawn and concluded from the study:

- Naringenin lowers down the level of Systolic blood pressure at 2nd and 4th week, this difference between Control and Naringenin treated rats was significant at a value of 0.053 and 0.04 respectively.
- Body weight analysis revealed that rats receiving Naringenin treatment were better in health as compared to control. First week analysis revealed that the difference between two groups was significantly different at a value of 0.04. The rats of treated groups were having higher weights.
- Corresponding results were observed for week four body weight analysis, It revealed that the control and treated groups are significantly different (p=00.2). The rats receiving Naringenin treatment were heavier (higher body weight) than the non-treated control.
- Treatment of Naringenin for duration of one week, lowered down heart rate significantly with a p value of 0.04 when compared with non-treated control.
- Similar pattern was observed for week 3rd and 4th where treated rats showed lower heart rate than control. The difference between control and Naringenin rats was significantly different at a value of 0.007 and 0.003.
- The assay involving enzyme Creatinine Phosphokinase (CPK) enabled us to know that the values of this enzyme in pg/nl are significantly lowered in Naringenin treated rats with a value of significance 0.001
- Narigenin is a useful agent in future for treatment of ischaemia related diseases in children also

In overall this study presented Flavonoid Naringenin as a potent bio-active molecule as a therapeutic strategy for CVD.

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