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Original Article

Study of Interactions between Monoherbal Formulation of *Arjuna* and *Aloe vera* in Isoproterenol Induced Cardiotoxicity Rat Model

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ABSTRACT

Introduction: Arjuna is used for its cardioprotective action while *Aloe vera* is herbal dietary supplement. Isoproterenol hydrochloride was administered subcutaneously to rats to induce myocardial infarction. **Objectives:** The given study was conducted to determine any pharmacodynamic interaction between marketed formulations i.e., Arjuna and *Aloe vera*. **Materials and Methods:** The varying tissue damage caused by Isoproterenol in different groups was confirmed from electrocardiogram (Heart rate, ST segment elevation time, QRS complex amplitude), levels of serum cardiac markers (creatine kinase, isoform of creatine kinase, Lactate dehydrogenase), blood electrolytes levels, by determining antioxidant enzymes activity (Superoxide dismutase, Catalase, Glutathione) and histopathological results. **Results:** The interaction group showed increased Heart rate, increased ST segment elevation time, decreased QRS complex; decreased antioxidant enzyme activity and increased levels of cardiac markers when compared to Arjuna group. The results were found to be statistically significant ($p<0.05$). **Conclusion:** Detrimental effect was found between two herbal formulations as a result of which the Cardioprotective effect of Arjuna was decreased when administered simultaneously with *Aloe vera*.

Keywords: Isoproterenol, *Aloe vera*, Arjuna, Myocardial infarction, Cardiotoxicity.

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INTRODUCTION

Herbal products are preferred by many patients and health care practitioners and about 70% of population worldwide makes use of herbal medicines for part of their primary health care.[1] Herbal preparations have many chemical components thus interaction among different herbal drugs is common and effects due to interaction among these components can be difficult to predict.[2] Simultaneous use of herbal drugs increases the potential of interaction between them. These effects due to interaction can be synergistic or antagonistic. Pharmacokinetic and pharmacodynamic interactions from herb-herb combinations have been described and documented in recent literature. Use of herbal supplements among people has increased within last few years and people prefer it due to lack of side effects.[3] Over the counter herbal medications are easily available and people take them without consulting medical practitioners such patients might use more than one herbal preparation without any knowledge about any interaction among those herbal preparations and the effects, which it may cause. Such simultaneous use of different herbal preparations can lead to herb-herb interactions, can affect the efficacy of drug, and can lead to severe adverse reactions.[4] Constipation is common gastrointestinal disorder in elderly patients. Most studies estimate the prevalence of constipation in the general population to be 16% worldwide (varies between 0.7% and 79%); whereas the prevalence of 33.5% was attributed to adults aged 60 to 110 years.[5] Prevalence increases with age and thus use of laxatives among elderly patients is common.[6] Aging affects functioning of organs. One of the systems affected is cardiovascular system. With age, heart loses its elasticity and its ability to respond to changes in blood pressure due to vascular stiffening, increased ventricular wall thickness and fibrosis.[7] Herbal cardioprotectives being considered safe are thus preferred by patients. To determine safety of herbal cardio protectives and herbal dietary supplement on concomitant use this study was done and any adverse effect due to interaction between two monoherbal formulations was determined from pharmacodynamic data. The formulations selected were herbal cardioprotective preparation i.e., Arjuna capsules and herbal dietary supplement i.e., *Aloe vera* capsules. The experimental model selected was Isoproterenol induced cardiotoxicity in Sprague-Dawley albino male rats.

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Mechanism of action of isoproterenol

According to reports, myocardial infarction induced by ISO causes a number of metabolic and morphologic abnormalities in the heart tissue of experimental animals that are identical to those seen in human myocardial infarction. The left ventricle's subendocardial area and the interventricular septum exhibit the greatest levels of ISO-induced necrosis. Rats receiving continuous infusions of ISO exhibit typical cardiac gene expression akin to that seen in cases of pressure overload-induced heart hypertrophy. One could mention the following among the many theories put forth to explain how isoproterenol causes myocardial damage: an imbalance between oxygen supply to and demand from cardiomyocytes internally, which is connected to myocardial hyperfunction resulting from an increase in both chronotropism and inotropism as well as hypotension in the coronary bed. Moreover, it is stated that the cell contains an elevated Ca++ overcharge. Also, that ion is connected to the progression of the events through the activation of the adenylate cyclase enzyme and the depletion of ATP levels. As a result of various isoproterenol-derived metabolic products as well as the production of free radicals, oxidative stress eventually increases.[8]

MATERIALS AND METHODS

Materials

Himalaya Arjuna capsules: Cardioprotective monoherbal preparation containing *Terminalia arjuna* extract and Nature's Flair *Aloe vera* capsules herbal dietary supplement containing *Aloe barbadensis* extract were used for study. Isoproterenol hydrochloride was purchased from Sigma-Aldrich. For enzyme assays and other tests, AR grade reagents were used. Tests for sodium, potassium, CK-MB, CK, LDH were performed using diagnostic kits.

Experimental animals

Sprague-Dawley albino male rats (250 g-300 g) were purchased from Bharat Serum Road no 27, Plot No. 371-372, Wagle Industrial Estate, Thane 400602. The study was conducted after approval of the Experimental protocol (IAEC/PR/APRIL2014-15/06) from Institutional Animal Ethics Committee (IAEC), Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai, India. Rats were housed in the animal house of Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai, India. Three rats per cage were housed in polypropylene cages. Corncob was used as bedding material for rats which was changed every 4 to 5 days. The animal house was maintained at an average temperature (24.0°C±2°C) and 30-70% RH, with 12 hr light-dark cycle. Animals were fed with commercial pellet diet (Amrut pellet) and water *ad libitum*. The animals were acclimatized for one week prior to the experiment. The experiments were carried out in accordance with the guidelines set by the Committee for Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Experimental groups

The study included four experimental groups each with six animals. Group 1 – Isoproterenol control received vehicle, Group 2- received *Aloe vera* (200 mg/kg/day),[9] Group 3- received Arjuna (600 mg/kg/day)[10] and Group 4 - received combination of *Aloe vera* (200 mg/kg/day)[9] and Arjuna (600 mg/kg/day)[10] from 1st to 12th day.

Dose preparation and administration

The capsule contents were triturated with 1% CMC in distilled water and administered with oral gavages to the respective groups.

Induction of myocardial infarction

Animals from all groups were challenged with Isoproterenol hydrochloride solution (150 mg/kg/mL)[11] subcutaneously on 9th and 10th day at interval of 24 hr.

Electrocardiogram (ECG) recordings

On the 10th day after Isoproterenol administration, animals were anesthetized using urethane (1.25 g/kg)[12] that was administered intraperitoneally. ECG was recorded through Lead II position using BIOPAC mp30 data acquisition system (BIOPAC system, Santa Barbara, CA. U.S.A.). Heart rate, QRS complex and ST segment elevation time were recorded.

Biochemical estimation

On 11th day, blood was collected from retro orbital sinus and was allowed to clot and then centrifuged; the serum was separated and was further used for determination of Serum Creatine Kinase (CK), Lactose Dehydrogenase (LDH), Creatine Kinase-MB (CK-MB).[13] On 12th day, immediately after scarification, heart was excised and washed with ice-cold normal saline. Parts of these tissues were stored in 10% formalin for histopathological evaluation and the remaining tissue was used for determination of Superoxide Dismutase (SOD), Catalase (CAT), GSH activity.[14] 10% w/v tissue homogenates were prepared and then centrifuged to obtain clear supernatant which was used to determine SOD,[15] CAT,[16] GSH activity[17] using standard UV spectroscopic method.

Gastrointestinal Transit

Animal's in-group 2, 3 and 4 were fasted for a period of 24 hr. On 12th day, 30 min after their daily oral treatment they were given 1 mL of charcoal suspension (3%) in normal saline orally. 30 min later all the animals were sacrificed using CO^2 euthanasia chamber; intestine was carefully excised and placed in 10% formalin to stop peristalsis and distance travelled by charcoal from pylorus to caecum was measured.

Histopathology

The heart was excised from animal of all groups and placed in 10% formalin for histopathological examination.

Data Analysis

The results were expressed as Mean±SEM (n=6). The given data were analyzed statistically using one-way ANOVA followed by Tukey's multiple comparison tests using GraphPad prism 6. The value of p<0.05 was considered significant.

RESULTS

Figure 1a and 1b represents the data from ECG recordings, which suggested that there was significant decrease in the QRS complex amplitude and increase in ST segment elevation time of animals from Arjuna and *Aloe vera* combination group as compared to animals from Arjuna group; while non-significant changes were observed as compared to Isoproterenol group. Also, there was significant increase in the heart rate of animals from Arjuna and *Aloe vera* combination group as compared to animals from Arjuna group; but not as high as that of heart rate of animals from Isoproterenol group.

Values are expressed as Mean±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Values are expressed as Mean±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Figure 2a represents the blood serum parameters, which suggested that there was increase in serum parameters in Arjuna and *Aloe vera* combination group and Isoproterenol group when compared to Arjuna group. Similarly, Figure 2b represents the increased blood electrolytes level of animals from the Arjuna and *Aloe vera* combination group as compared to Isoproterenol group. And it seemed to be decreased significantly as compared to Arjuna group.

Values are expressed as Mean±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Values are expressed as Mean±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Figure 3 represents gastrointestinal transit, which suggested that in *Aloe vera* group maximum distance was travelled by charcoal meal as compared to Arjuna group but in Interaction group minimum distance was travelled by charcoal meal as compared to Arjuna.

Values are expressed as Mean±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Figure 4 represents tissue parameters for myocardial infarction in heart and it was found that there was decrease in SOD, CAT and GSH levels in both Isoproterenol and Interaction group. Whereas these levels were found to be increased in Arjuna and *Aloe vera* group respectively.

Values are expressed as Mean ±SEM (n=6), Significance was determined by one-way ANOVA followed by Tukey's multiple comparison. p< 0.05 * indicates there is significant difference when compared with Isoproterenol Control Group; p< 0.05 # indicates there is significant difference when compared with Arjuna Group.

Histopathological investigation

Figure 5 represents the histopathological images of Heart. The isoproterenol group showed moderately multifocal myocytic necrosis of mild degree with loss of sarcoplasm and minimal

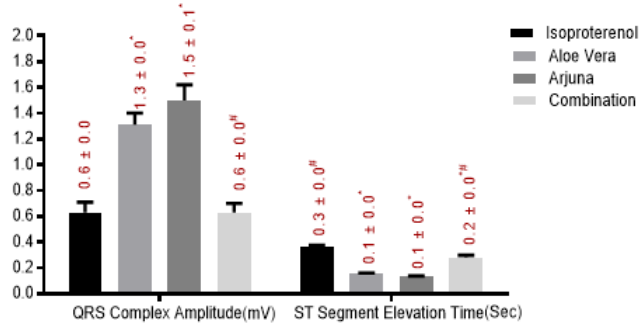

Figure 1a: Electrocardio graphical recordings: QRS complex amplitude and ST segment elevation time.

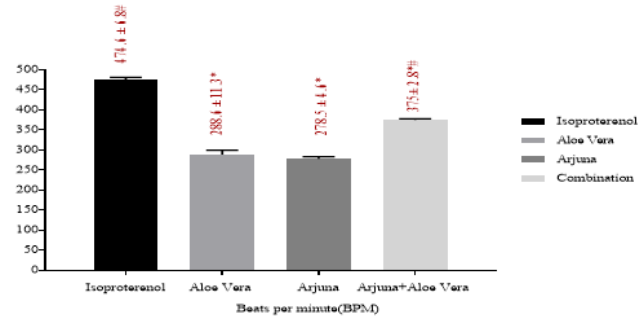

Figure 1b: Electrocardio graphical recordings: Heart rate.

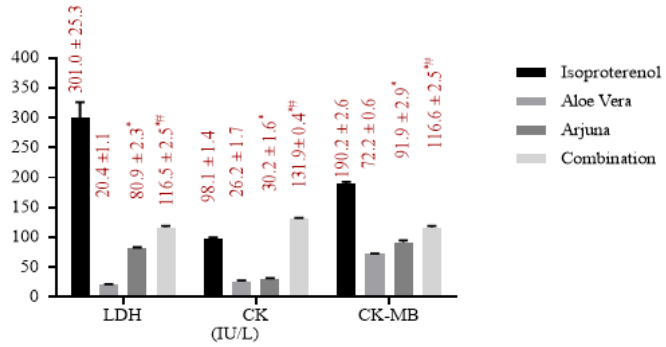

Figure 2a: Blood serum parameters.

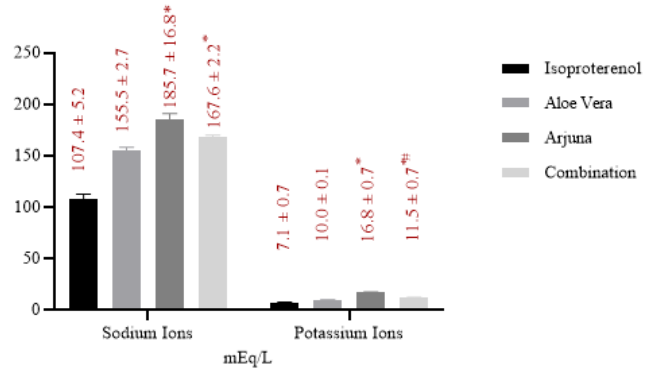

Figure 2b: Blood electrolytes levels.

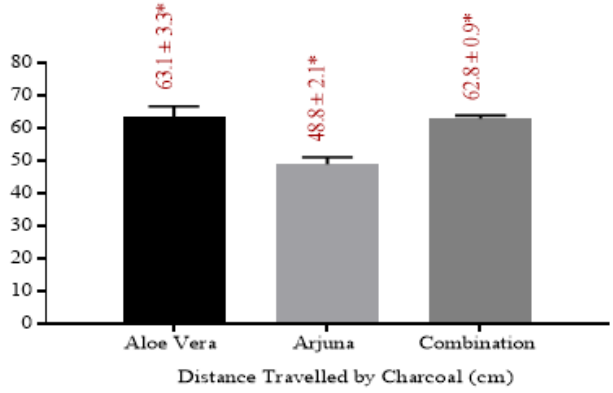

Figure 3: Gastrointestinal transit.

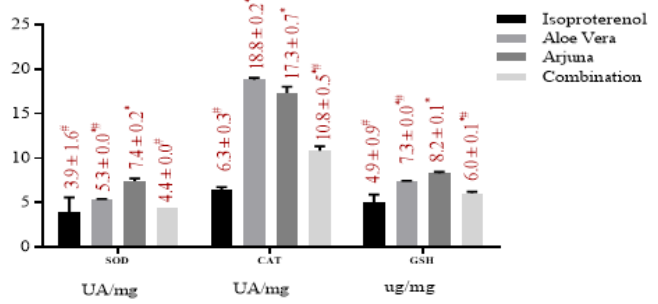

Figure 4: Tissue parameters for myocardial infarction: heart.

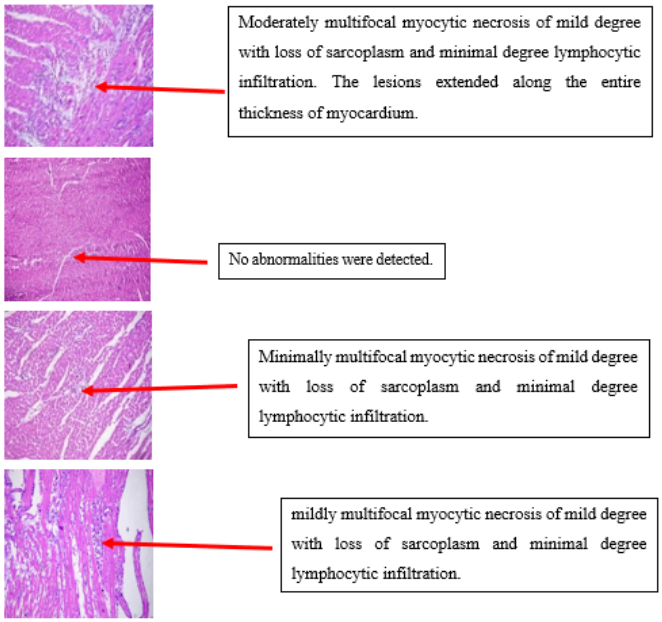

Figure 5: Histopathological images of heart (a) Isoproterenol group, (b) *Aloe vera* group, (c) Arjuna group, (d) Arjuna and *Aloe vera* combination group.

degree lymphocytic infiltration. The lesions extended along the entire thickness of myocardium. There were no abnormalities found in the anatomy of heart of *Aloe vera* control group. In Arjuna group minimally multifocal myocytic necrosis of mild degree with loss of sarcoplasm and minimal degree lymphocytic infiltration was found. In the combination group there was mild multifocal myocytic necrosis of mild degree with loss of sarcoplasm and minimal degree lymphocytic infiltration.

DISCUSSION

This study was conducted to determine any change in pharmacodynamic effects due to interaction between marketed herbal cardioprotective formulation (Arjuna) (600 mg/kg/day) and marketed herbal laxative formulation (*Aloe vera*) (200 mg/kg/day) on concomitant oral administration in Sprague Dawley rats. On 9th and 10th day of the study isoproterenol hydrochloride (150 mg/kg/mL) in normal saline was administered by subcutaneous route to induce myocardial infarction. This myocardial damage resulted in changes in cardiac parameters (Heart rate, ST segment, QRS complex) which were determined by recording ECG. QRS complex represents ventricular depolarization. Increase in amplitude indicates increased left ventricular function, which was observed in Arjuna control whereas a decrease in amplitude was observed in Isoproterenol and Arjuna and *Aloe vera* combination group. ST segment represents the isoelectric period, at this time the ventricle is in depolarized state. Increase in ST segment elevation

time is an indication of myocardial injury, which was observed in Isoproterenol and *Arjuna* and *Aloe vera* combination group. Isoproterenol has positive chronotropic effect thus heart rate was found to be increased in Isoproterenol and Arjuna and *Aloe vera* combination group whereas Arjuna group showed normal heart rate compared to Isoproterenol group. Increased heart rate affects the blood supply to organs. The difference in data within the groups indicated the varying damage caused by Isoproterenol in different groups, which clearly proves the interaction between the two drugs. Isoproterenol hydrochloride is beta 1 receptor agonist having positive chronotropic and positive ionotropic effect. The myocardial damage caused by Isoproterenol hydrochloride is due to increased oxidative metabolism to a level that exceeds the amount of oxygen available to the myocyte, resulting in ischemic damage, the damage being like myocardial infarction. Isoproterenol was responsible for increase in heart rate, decreased QRS complex amplitude and an increase in ST segment elevation time and decrease in antioxidant enzymes (SOD, GSH and CAT) whereas an increase in serum parameters (CK, CK-MB and LDH) in animals from Isoproterenol group.[15-18] The animals in Arjuna control group showed improved cardiac parameters reflecting its cardioprotective action. Arjuna contains arjunolic acid, which is potent antioxidant, and free radical scavenger prevented decrease in antioxidant enzymes levels in animals from Arjuna control group. Free radical scavenging activity is attributed to carboxylic hydrogen in arjunolic acid, which can be easily removed by any free radical. Its blood pressure lowering effect, prevention from myocardial necrosis, platelet aggregation activity has been proven experimentally thus explaining its Cardioprotective effect.[19,20] Animals in Arjuna and *Aloe vera* combination group showed effect on cardiac parameters similar to those in Isoproterenol control group; indicating pharmacodynamic interaction between the two monoherbal formulations. Laxation can be brought about by increase in water content or by stimulation of peristalsis in the large intestine. *Aloe vera* contains barbaloin which decomposes to aloe-emodin-9-anthrone[21] in intestine which causes an increase in water content of the intestine by two mechanisms inhibition of rat colonic sodium, potassium adenosine triphosphatase and increase of paracellular permeability across the colonic mucosa, this results in excess loss of sodium and potassium.[22] These ions play an important role in normal cardiac function, inappropriate proportion of these ions affects heart contractions which can become irregular and weaker increasing cardiac failure risk, depletion of these ions from blood was confirmed by sodium potassium test. Their low levels had an additive effect on cardiac damage, which masked cardioprotective action of Arjuna. Hence, the results of Isoproterenol, Arjuna, and *Aloe vera* combination groups were closer. Catalase, GSH and Superoxide Dismutase which are anti-oxidant enzymes provide protection against free radicals generated during stress, change in levels of these enzymes indicate the degree of oxidative stress on an organ. Levels of these enzymes in Isoproterenol group and *Arjuna* and *Aloe vera* combination group were similar thus indicating interaction, which was detrimental. Whereas, *Arjuna* group showed better enzyme levels compared to Isoproterenol, *Arjuna*, and *Aloe vera* combination group. CK and CK-MB are mitochondrial enzymes whereas LDH is present in cytoplasm, these enzymes are important in cellular energy metabolism. Disruption of cell membranes due to injury causes release of these enzymes into systemic circulation. LDH, CK and CK-MB levels thus increase during tissue injury. Thus, elevated levels in serum indicate tissue injury. CK is located in skeletal muscle, myocardium and brain, whereas CK-MB is an isoenzyme found predominantly in myocardium and LDH is located in myocardium, skeletal muscles, liver, lung, lymphnodes, spleen, erythrocyte, leucocytes and platelets. Elevated levels of this enzyme in serum thus indicate cell damage. Levels of these enzymes were found to be higher in Isoproterenol group as well as interaction group whereas *Arjuna* group showed lower levels of these enzymes because of its cardioprotective action.

CONCLUSION

The conducted study thus proves experimentally that the simultaneous use of herbal cardioprotective and herbal laxative is detrimental and thus its simultaneous use should be avoided. The loss of electrolytes due to laxative action of *Aloe vera* increases the myocardial damage in case of oxidative stress even when cardioprotective drug is being consumed masking its cardioprotective effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CKMB: Creatine Kinase Myoglobin Binding; **CK:** Creatine Kinase; **LDH:** Lactose Dehydrogenase; **IAEC:** Institutional Animal Ethics Committee; **CPCSEA:** Committee for Purpose

of Control and Supervision on Experiments on Animals; **CMC:** Carboxymethyl Cellulose; **ECG:** Electro Cardio Gram; **SOD:** Super Oxide Dismutase; **CAT:** Catalase; **GSH:** Reduced form of Glutathione.

SUMMARY

Herbal preparations have many chemical components thus interaction among different herbal drugs is common. Simultaneous use of herbal drugs increases the potential of interaction between them. Such simultaneous use of different herbal preparations can lead to herb-herb interactions affecting the drug efficacy, which may lead to severe adverse reactions or therapeutic failure.

Aging affects functioning of organs. One of the systems affected is cardiovascular system. To determine safety of herbal cardioprotectives and herbal dietary supplement on concomitant use, this study was done and pharmacodynamics interaction between two monoherbal formulations was determined. The formulations selected were herbal cardioprotective preparation i.e., Arjuna capsules and herbal dietary supplement i.e., *Aloe vera* capsules. The experimental model selected was isoproterenol induced cardiotoxicity in Sprague-Dawley albino male rats.

The study included four experimental groups each with six animals such as Isoproterenol control received vehicle, *Aloe vera* (200 mg/kg/day), Arjuna (600 mg/kg/day) and combination of *Aloe vera* (200 mg/kg/day) and Arjuna (600 mg/kg/day). Treatment was administered to the respective groups via oral gavages from 1st to 8th day. Isoproterenol hydrochloride (150 mg/kg/mL) in normal saline was administered subcutaneously on the 9th and 10th days to cause myocardial infarction. The rats were given urethane anesthesia on the 11th day, and heart rate, QRS complex, and ST-segment elevation time was recorded. Blood was also drawn from the retro-orbital sinus on the 11th day, and the levels of serum Creatine Kinase (CK), Lactose Dehydrogenase (LDH), and Creatine Kinase Myoglobin Binding were then determined (CK-MB). The heart was removed and stored on the 12th day, right after the sacrifice. Parts of these heart tissues were used for histopathological evaluation. 10% w/v heart tissue homogenates were prepared and then centrifuged to obtain clear supernatant which was used to determine SOD, CAT, GSH activity using standard UV spectroscopic method.

Ventricular depolarization is represented by the QRS complex. The isoelectric period, which is represented by the ST segment, is when the ventricle is depolarized. In contrast to the Arjuna control group, which showed an increase in amplitude, the Arjuna and *Aloe vera* combination group showed a decrease in Amplitude, an increase in ST-Segment Elevation Time, and an increase in heart rate. Compared to the Isoproterenol group, the Arjuna group showed a normal heart rate. The degree of oxidative stress on an organ is indicated by changes in the levels of CAT, GSH, and SOD. When compared to the Isoproterenol, Arjuna, and *Aloe vera* combination group, the Arjuna groups showed better enzyme levels. Consequently, elevated serum levels of CK, CK-MB, and LDH indicate cell damage. Levels of these enzymes were found to be higher in the Isoproterenol group as well as the combination group whereas the Arjuna group showed lower levels of these enzymes because of its cardioprotective action.

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