

A Research Study into the Interactions Between the Monoherbal Formulations of *Arjuna* and *Aloe vera* in a Rat Model of Isoproterenol-Induced Cardiotoxicity

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Abstract

Introduction: *Aloe vera* is an herbal dietary supplement, and *arjuna* is used for its cardioprotective properties. Rats were given isoproterenol hydrochloride subcutaneously to cause myocardial infarction.

Purpose: The purpose of the study was to identify any potential pharmacodynamic interactions between the commercially available formulations of *Aloe vera* and *arjuna*. **Materials and Procedures:** The electrocardiogram (heart rate, ST segment elevation time, QRS complex amplitude), serum cardiac markers (creatinine kinase, isoform of creatine kinase, lactate dehydrogenase), blood electrolyte levels, antioxidant enzyme activity (superoxide dismutase, catalase, glutathione), and histopathological findings all confirmed the different tissue damage caused by isoproterenol in different groups. **Results:** In comparison to the *Arjuna* group, the interaction group displayed elevated cardiac markers, decreased antioxidant enzyme activity, elevated heart rate, increased ST segment elevation time, and decreased QRS complex. The findings showed statistical significance ($p < 0.05$). **Conclusion:** When *Arjuna* and *Aloe vera* were taken together, the cardioprotective effect of *Arjuna* was diminished due to the detrimental effect between the two herbal formulations.

Keywords: Isoproterenol, *Aloe vera*, *Arjuna*, myocardial infarction, cardiotoxicity

INTRODUCTION

Many patients and medical professionals prefer herbal products, and roughly 70% of people worldwide use herbal medicines as part of their primary care [1]. Because herbal preparations contain a variety of chemical components, it is common for various herbal drugs to interact with one another, and the effects of these interactions can be unpredictable [2]. The possibility of an interaction between herbal medications is increased when they are used concurrently. These interactions can have either antagonistic or synergistic effects. In recent literature, pharmacokinetic and pharmacodynamic interactions resulting from herb-herb combinations have been described and documented. People have been using herbal supplements more frequently in recent years because they don't have any negative side effects [3]. Herbal remedies are readily available over the counter, and many people use them

without first seeing a doctor. These patients may use multiple herbal preparations without realizing it, and pharmacodynamic data revealed any negative effects resulting from the interaction of two monoherbal formulations. Herbal dietary supplements, such as *Aloe vera* capsules, and herbal cardioprotective preparations, such as *Arjuna* capsules, were the formulations chosen. Isoproterenol-induced cardiotoxicity in male Sprague-Dawley albino rats was the experimental model chosen to investigate potential interactions and effects between those herbal preparations. Using various herbal preparations at the same time can result in serious adverse reactions, herb-herb

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interactions, and reduced drug efficacy [4]. In older patients, constipation is a common gastrointestinal condition. According to most studies, the prevalence of constipation in the general population is 16% worldwide (ranging from 0.7% to 79%); in contrast, adults aged 60 to 110 years were found to have a prevalence of 33.5% [5]. Elderly patients frequently use laxatives because the prevalence rises with age. Organ function is impacted by aging. The cardiovascular system is among the systems impacted. As we age, vascular stiffening, thicker ventricular walls, and fibrosis cause the heart to lose its elasticity and its capacity to react to variations in blood pressure [6]. Patients prefer herbal cardioprotective because they are thought to be safe. This study was conducted to ascertain the safety of using herbal dietary supplements and cardioprotective concurrently.

MECHANISM OF ACTION OF ISOPROTERENOL

It has been reported that myocardial infarction induced by ISO results in several morphologic and metabolic abnormalities in experimental animals' heart tissue that are identical to those observed in myocardial infarction in humans. The interventricular septum and the subendocardial region of the left ventricle show the highest degrees of ISO-induced necrosis. Rats given continuous ISO infusions show normal cardiac gene expression, like that observed in heart hypertrophies brought on by pressure overload [7]. Among the numerous hypotheses proposed to explain how isoproterenol damages the heart, the following could be mentioned: an imbalance between the internal oxygen supply to and demand from cardiomyocytes, which is linked to myocardial hyperfunction brought on by an increase in both chronotropism and inotropism as well as hypotension in the coronary bed. Additionally, the cell is said to have a high Ca^{++} overcharge. Additionally, the adenylate cyclase enzyme's activation and the ATP levels' depletion are linked to the events' progression. Oxidative stress eventually rises due to the generation of free radicals and different metabolic products derived from isoproterenol [8].

MATERIALS AND METHODS

Materials

Himalaya *Arjuna* capsules: the research used Nature's Charm *Aloe vera* capsules, an herbal dietary supplement containing *Aloe barbadensis* extract, and a cardioprotective monoherbal preparation containing *Terminalia Arjuna* extract. Sigma-Aldrich was the supplier of isoproterenol hydrochloride. AR grade reagents were utilized for enzyme assays and other tests. Diagnostic kits were used to conduct tests for potassium, sodium, CK-MB, CK, and LDH.

Experimental Animals

We bought male Sprague-Dawley albino rats weighing between 250 and 300 grams from the Kalka Institute for Research and Advanced Studies in Meerut. Following approval of the experimental protocol (IAEC/PR/APRIL2014-15/06) by the Kalka Pharmacy Institute for Advanced Studies' Institutional Animal Ethics Committee (IAEC), the study was carried out in Meerut, India. The Kalka Pharmacy Institute for Advanced Studies in Meerut kept rats in its animal house. The cages were made of polypropylene and held three rats each. Rats were housed on corncob, which was replaced every four to five days. The animal house had a 12-hour light-dark cycle, an average temperature of $24.0^{\circ}\text{C} \pm 2^{\circ}\text{C}$, and a relative humidity of 30–70%. The animals were given water at will and a commercial pellet diet (Amrut pellet). A week before the experiment, the animals were acclimated. Following the rules established by the Committee for Purpose of Control and Supervision on Experiments on Animals (CPCSEA), the experiments were conducted.

Experimental Group

Four experimental groups, each with six animals, were included in the study. Group 2 received *Aloe vera* (200 mg/kg/day), Group 1 received a vehicle containing isoproterenol, and Group 9 *Arjuna* (600 mg/kg/day) was given to Group 3. Groups 10 and 4 were given a combination of *Aloe vera* (200 mg/kg/day) [9] and *Arjuna* (600 mg/kg/day) [10] from the first to the twelfth day.

Dose Preparation and Administration

The contents of the capsules were given to the corresponding groups orally via gavage after being triturated with 1% CMC in distilled water.

Induction of Myocardial Infarction

Isoproterenol hydrochloride solution (150 mg/kg/mL) [11] was administered subcutaneously to animals in all groups on days 9 and 10, separated by 24 hours.

Electrocardiogram (ECG) Recordings

On day 10, following the administration of isoproterenol, urethane (1.25 g/kg) [12] was injected intraperitoneally to put the animals to sleep. A BIOPAC mp30 data acquisition system (BIOPAC system, Santa Barbara, CA, U.S.A.) was used to record the ECG through the Lead II position. We measured the ST segment elevation time, heart rate, and QRS complex.

Biochemical Estimation

On day 11, blood was drawn from the retroorbital sinus, allowed to clot, and then centrifuged. The serum was separated and used to measure the levels of lactose dehydrogenase (LDH), serum creatine kinase (CK), and creatine kinase-MB (CK-MB) [13]. The heart was removed on the twelfth day, right after scarification, and cleaned with ice-cold normal saline. For histopathological analysis, portions of these tissues were preserved in 10% formalin; the remaining tissue was used to measure the activity of GSH, Catalase, and Superoxide Dismutase (SOD). SOD, CAT, and GSH activity were measured using the standard UV spectroscopic method after preparing tissue homogenates at a concentration of 10% w/v and centrifuging the resulting clear supernatant.

Gastrointestinal Transit

The animals in groups two, three, and four were fasted for twenty-four hours. They received 1 milliliter of a 3% charcoal suspension in normal saline orally on the twelfth day, half an hour after their daily oral treatment. After 30 minutes, all the animals were killed in a CO₂ euthanasia chamber; the distance traveled by charcoal from the pylorus to the caecum was measured, and the intestine was carefully removed and submerged in 10% formalin to stop peristalsis.

Histopathology

All animals' hearts were removed, and they were then preserved in 10% formalin for histopathological analysis.

Data Analysis

Mean \pm SEM was used to express the results (n = 6). One-way ANOVA and Tukey's multiple comparison tests were used to statistically analyze the provided data using GraphPad Prism 6. A p-value of less than 0.05 was deemed significant.

RESULTS

Figures 1(a) and (b) show the ECG recording data, which indicated that the animals in the *Arjuna* and *Aloe vera* combination group had a significant decrease in the QRS complex amplitude and an increase in the ST segment elevation time when compared to the animals in the *Arjuna* group. However, there were no significant changes when compared to the Isoproterenol group. Additionally, animals in the *Arjuna* and *Aloe vera* combination group had a significantly higher heart rate than those in the *Arjuna* group, though it was still lower than that of the animals in the isoproterenol group.

Values are presented as Mean \pm SEM (n = 6). Tukey's multiple comparison was used to determine significance after a one-way ANOVA. Significant differences with respect to the Isoproterenol Control Group and the *Arjuna* Group are indicated by p < 0.05* and p < 0.05#, respectively.

Figure 2(a) represents the blood serum parameters, which indicated that, in comparison to the *Arjuna* group, the serum parameters in the *Aloe vera* and *Arjuna* combination group and the isoproterenol group had increased. In the same way, Figure 2(b) represents how animals in the *Arjuna* and *Aloe vera* combination group had higher blood electrolyte levels than those in the isoproterenol group. Additionally, it appeared to have dropped considerably in comparison to the *Arjuna* group.

Values are presented as Mean ± SEM (n = 6). Tukey’s multiple comparison was used to determine significance after a one-way ANOVA. Significant differences with respect to the Isoproterenol Control Group and the *Arjuna* Group are indicated by p < 0.05* and p < 0.05#, respectively.

Figure 3 represents gastrointestinal transit, indicating that the *Aloe vera* group traveled the greatest distance using charcoal meal in comparison to the *Arjuna* group, while the Interaction group traveled the smallest distance using charcoal meal in comparison to the *Arjuna* group.

Values are presented as Mean ± SEM (n = 6). Tukey’s multiple comparison was used to determine significance after a one-way ANOVA. Significant differences with respect to the Isoproterenol Control Group and the *Arjuna* Group are indicated by p < 0.05* and p < 0.05#, respectively.

Figure 4 represents tissue parameters for myocardial infarction in the heart, and it was discovered that the Isoproterenol and Interaction groups had lower levels of SOD, CAT, and GSH. In contrast, it was discovered that the *Aloe vera* and *Arjuna* groups had higher levels of these substances, respectively.

Values are presented as Mean ± SEM (n = 6). Tukey’s multiple comparison was used to determine significance after a one-way ANOVA. Significant differences with respect to the Isoproterenol Control Group and the *Arjuna* Group are indicated by p < 0.05* and p < 0.05#, respectively.

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

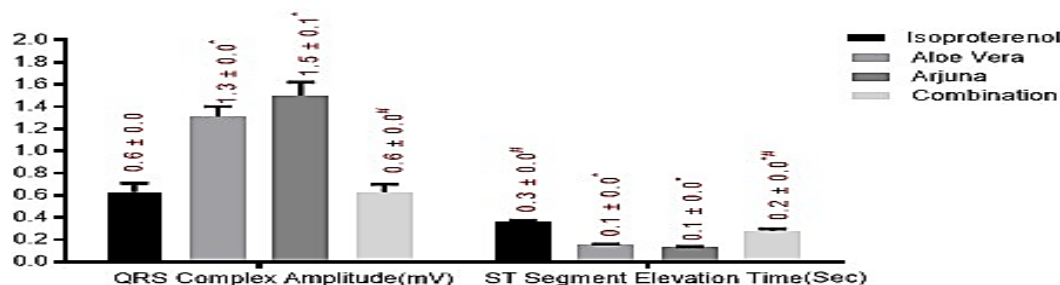


Figure 1(a). Electro cardio graphical recordings: QRS complex amplitude and ST segment elevation time.

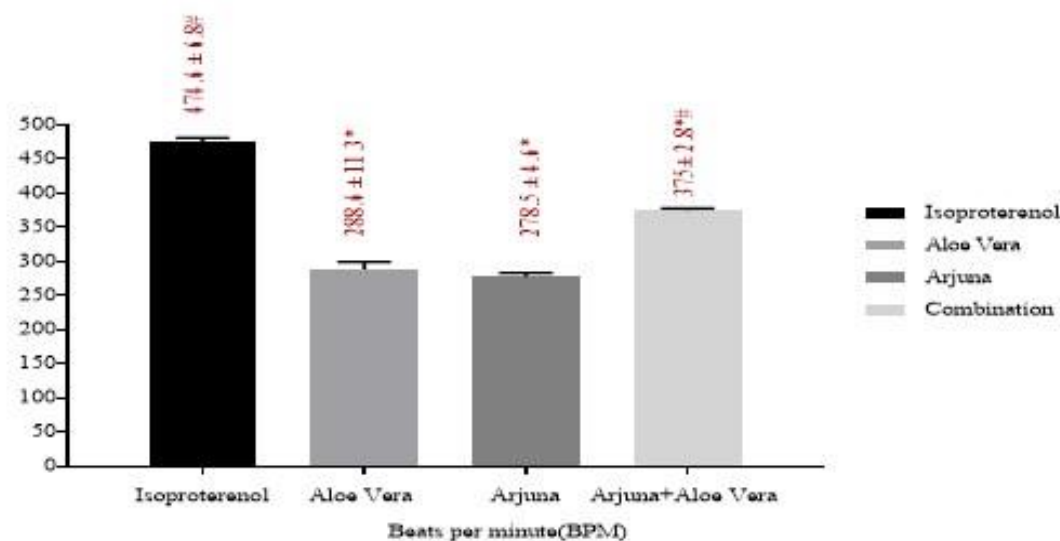


Figure 1(b). Electrocardio graphical recordings: Heart rate.

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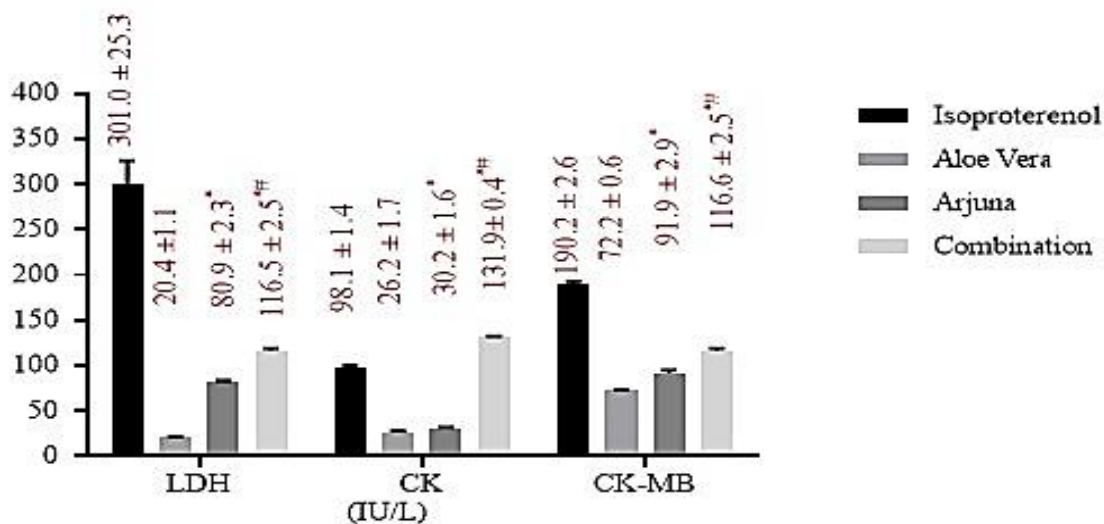


Figure 2(a). Blood serum parameters.

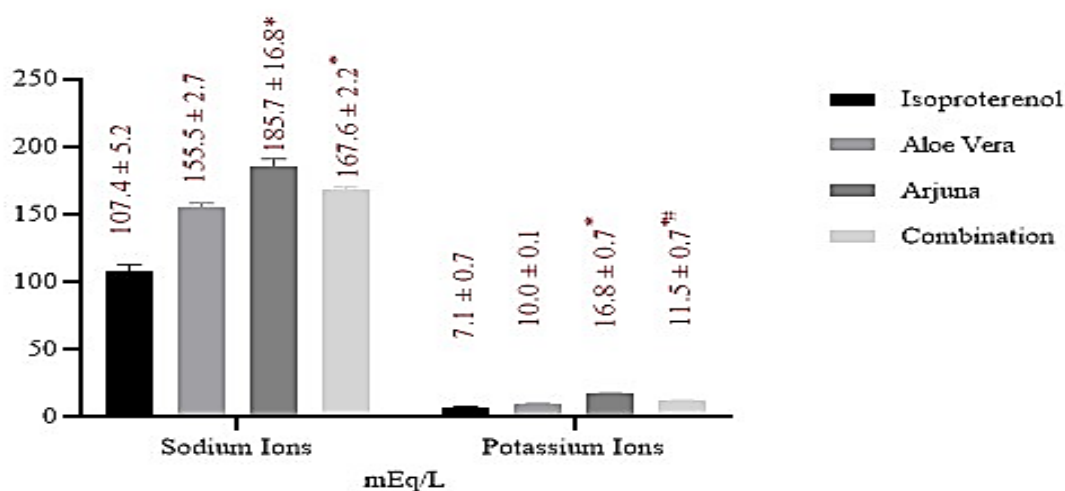


Figure 2(b). Blood electrolytes levels.

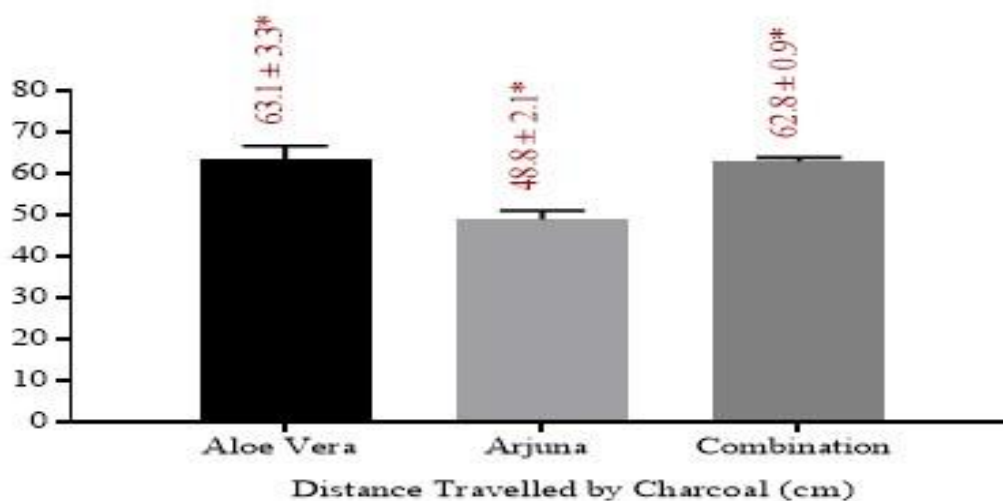


Figure 3. Gastrointestinal transit.

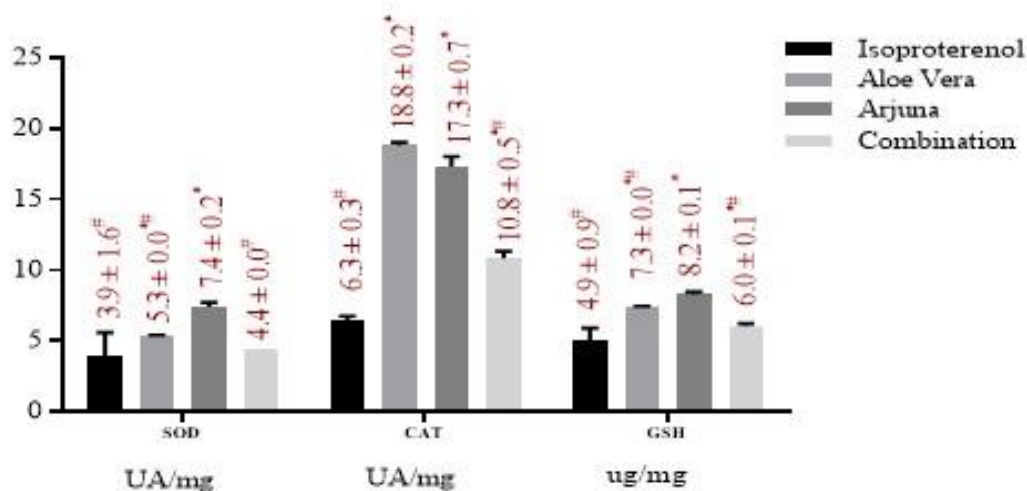


Figure 4. Tissue parameters for myocardial infarction: heart.

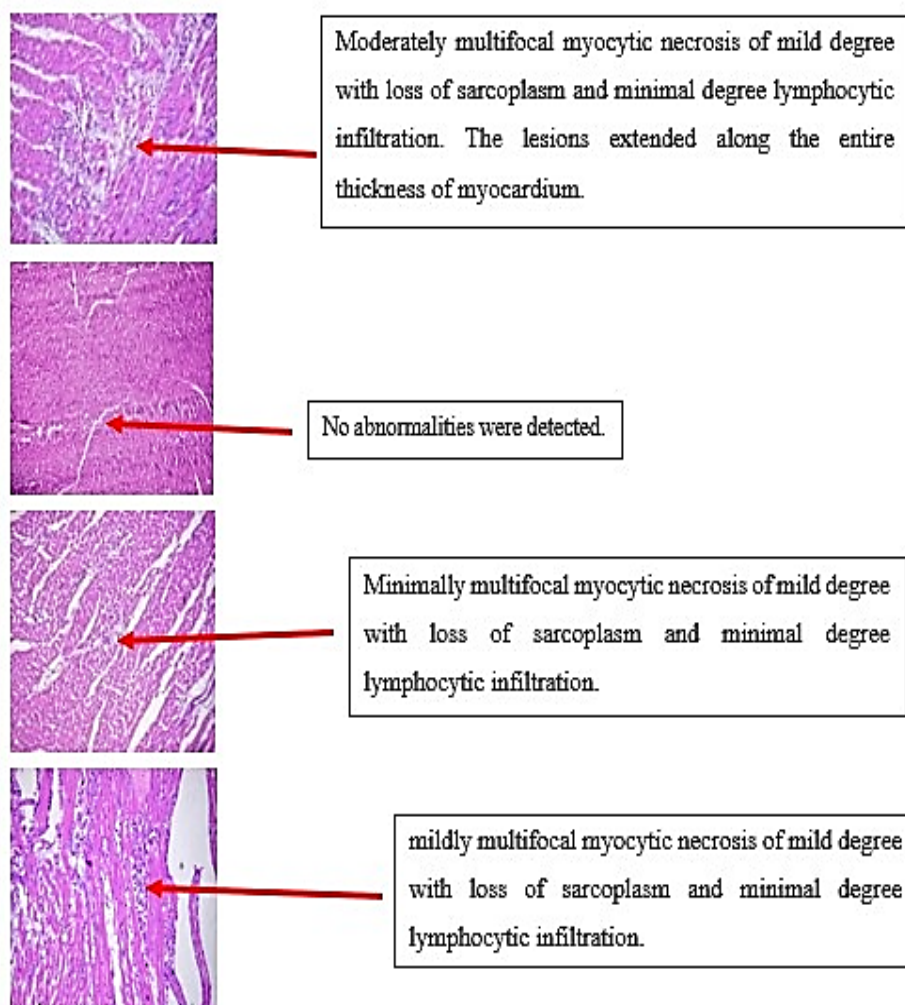


Figure 5. Histopathological images of heart (a) Isoproterenol group, (b) *Aloe vera* group, (c) *Arjuna* group, (d) *Arjuna* and *Aloe vera*.

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DISCUSSION

In this study, the marketed herbal laxative formulation (*Aloe vera*) (200 mg/kg/degree lymphocytic infiltration) and the marketed herbal cardioprotective formulation (*Arjuna*) (600 mg/kg/day) were compared for any changes in pharmacodynamic effects. The lesions were found throughout the myocardium's thickness. No anomalies were discovered in the *Aloe vera* control group's cardiac anatomy. A mild case of multifocal myocytic necrosis with sarcoplasm loss and a low level of lymphocytic infiltration was observed in the *Arjuna* group. Sarcoplasm loss and mild multifocal myocytic necrosis with minimal lymphocytic infiltration were observed in the combination group.

The study's 9th and 10th days involved the subcutaneous administration of isoproterenol hydrochloride (150 mg/kg/mL) in normal saline to cause myocardial infarction. By recording the ECG, it was possible to determine how this myocardial damage affected the cardiac parameters (heart rate, ST segment, and QRS complex). Ventricular depolarisation is represented by the QRS complex. Increased left ventricular function is indicated by an increase in amplitude, which was seen in the *Arjuna* control group while the Isoproterenol and *Arjuna* and *Aloe vera* combination groups showed a decrease in amplitude. The isoelectric period is represented by the ST segment, during which the ventricle is depolarized. Myocardial injury is indicated by an increase in ST segment elevation time, which was seen in the groups that took isoproterenol and *Arjuna* and *Aloe vera*. Since isoproterenol has a positive chronotropic effect, it was discovered that the heart rate of the groups taking it and *Arjuna* and *Aloe vera* together increased, while the heart rate of the *Arjuna* group was normal in comparison to the isoproterenol group. The blood flow to organs is impacted by elevated heart rate. It is evident that the two medications interact because the data within the groups showed that isoproterenol caused different amounts of damage in each group. Beta 1 receptor agonist isoproterenol hydrochloride has both positive chronotropic and positive inotropic effects. Isoproterenol hydrochloride causes ischemic damage, which is similar to myocardial infarction, in the heart by increasing oxidative metabolism to a level higher than the amount of oxygen available to the myocyte. In animals from the isoproterenol group, isoproterenol caused an increase in heart rate, a decrease in the amplitude of the QRS complex, an increase in the ST segment elevation time, and a decrease in antioxidant enzymes (SOD, GSH, and CAT). In contrast, the animals' serum parameters (CK, CK-MB, and LDH) increased [14–18]. The cardioprotective effect of *Arjuna* was demonstrated by the animals in the control group, who displayed improved cardiac parameters. Arjunolic acid, a strong antioxidant found in *Arjuna*, and free radical scavenger stopped the antioxidant enzyme levels in the *Arjuna* control group from dropping. Because any free radical can readily remove the carboxylic hydrogen in arjunolic acid, it is thought to have free radical scavenging activity. Its cardioprotective effect can be explained by experimentally proving its ability to lower blood pressure, prevent myocardial necrosis, and inhibit platelet aggregation activity. [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. A rise in water content or an increase in the large intestine's peristalsis can both cause laxation. By inhibiting rat colonic sodium and potassium adenosine triphosphatase and increasing paracellular permeability across the colonic mucosa, barbaloin, which is found in *Aloe vera*, breaks down to aloe-emodin-9-anthrone [21] in the intestine, increasing the water content of the intestine and causing excessive sodium and potassium loss [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 antioxidant 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 in skeletal muscle, myocardium and brain, whereas CK-MB is an isoenzyme found predominantly in myocardium and LDH is 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.

CONCLUSIONS

Thus, the study's experimental findings demonstrate that using herbal laxatives and cardioprotective at the same time is harmful and should be avoided. Even when a cardioprotective medication is taken, its cardioprotective effects are obscured by the electrolyte loss caused by *Aloe vera*'s laxative action, which increases myocardial damage in cases of oxidative stress.

Acknowledgment

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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 Cardiogram

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. There is a greater chance of an interaction when herbal medications are used concurrently. When several herbal preparations are used at the same time, there may be interactions between the herbs that impact the effectiveness of the medication, potentially resulting in serious side effects or therapeutic failure.

Organ function is impacted by aging. The cardiovascular system is among the systems impacted. This study examined the pharmacodynamic interactions between two monoherbal formulations to assess the safety of herbal cardioprotective and herbal dietary supplements when used concurrently. Herbal dietary supplements, such as *Aloe vera* capsules, and herbal cardioprotective preparations, such as *Arjuna* capsules, were the formulations chosen. Isoproterenol-induced cardiotoxicity in male Sprague-Dawley albino rats was the chosen experimental model.

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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