Effect of ayurvedic preparation 'Mrityunjay' in digoxin-induced arrhythmic rats

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Mrityunjay is a plant based ayurvedic preparation which is used in the treatment of high blood pressure as well as other cardiovascular diseases. It comprises of significant cardioprotective constituents. This study was conducted to evaluate the effect of Mrityunjay on digoxin-induced arrhythmia and lipid profile in rats. Rats were orally pre-treated with Mrityunjay at the doses of 0.28 and 2.8 mL/kg b.w. for consecutive 35 days through the oral route. On the 36th day, the rats were given a bolus dose of digoxin (20 mg/kg b.w., i.p.). Electrocardiogram along with heart rate were taken for an hour after digoxin administration and serum lipid profile was measured. The digoxin administration caused severe arrhythmia in rats. Mrityunjay significantly (p<0.05) inhibited digoxin-induced arrhythmia at both dose levels. In addition, it caused a significant (p<0.05) decrease in total cholesterol, low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol levels in blood serum. The study revealed that the ayurvedic preparation Mrityunjay possesses significant anti-arrhythmic activity against digoxin-induced arrhythmia. It also has a significant hypocholesterolemic effect.

Key words: Mrityunjay, ayurvedic preparation, cardioprotection, digoxin-induced arrhythmia, electrocardiography (ECG), lipid profile.

INTRODUCTION

Cardiovascular diseases (CVDs) are one of the major causes of mortality in the world (Zheng et al., 2013). As proclaimed by World Health Organization (WHO), CVDs were the leading non-communicable disease (NCD) in 2012 which caused 17.5 million, or 46% of NCD deaths (Mendis et al., 2015). In recent times, WHO has been giving emphasis on the concomitant use of traditional formulations, which are largely based on plant materials, to ensure total health coverage among herbal remedies; use of the ayurvedic system of medicine is prevalent in Bangladesh. Patients due to their poor economic condition depend on cost effective and affordable herbal drugs that are being used traditionally for centuries (Vogel et al., 2005). Ayurvedic products may exert

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significant therapeutic effects on the cardiovascular system (Lodha and Bagga, 2000). It has been found that there is a large demand for ayurvedic drugs for the remedies of CVDs. However, clinical applications of ayurvedic preparations are being thwarted due to their lack of quality, toxicological and pharmacological evidence (Chandra, 2016). Hence, WHO has emphasized the evaluation of quality, safety and therapeutic efficacy of ayurvedic preparations (Chaudhary and Singh, 2001).

Mrityunjay is a plant-based ayurvedic preparation which is used for the treatment of high blood pressure as well as other CVDs, according to Bangladesh National Formulary of Ayurvedic Medicine. The preparation contains root extracts of *Rauwolfia serpentina* L. (family: Apocynaceae), *Withania somnifera* L. (Solanaceae), *Glycyrrhiza glabra* L. (Fabaceae), *Glycyrrhiza glabra* L. (Fabaceae), *Acorus calamus* L. (Acoraceae), *Roscoea purpurea* Sm. (Zingiberaceae), bark extract of *Terminalia arjuna* Roxb. (Combretaceae), fruit extracts of *Terminalia chebula* Retz., *Terminalia bellirica* Roxb. (Combretaceae), *Phyllanthus emblica* L. (Phyllanthaceae), wood extract of *Acacia catechu* L.f. (Mimosaceae), a whole plant extract of *Tragia involucrate* L. (Euphorbiaceae), spikenard of *Nardostachys jatamansi* (Caprifoliaceae) and Jaggery (Anonymous, 1992).

*R. serpentina* is a medicinally important herb which is extensively used in the treatment of hypertension and psychotic disorders including anxiety, insanity, insomnia, schizophrenia, etc (Qureshi and Udani, 2009; Mashour et al., 1998). *Invivo* study revealed that methanol extract of *R. serpentina* may exert significant hypolipidemic and hypoglycemic activities (Qureshi and Udani, 2009). The main compound of *R. serpentina*, ajmaline, has been found to alleviate digoxin toxicity (Obayashi et al., 1976). The cardiogenic effect of the plant *T. arjuna* is evident in the ayurveda (Tripathi et al., 1996). The bark of the plant is used as anti-ischemic and cardioprotective (Bone and Morgan, 1996). *T. arjuna* bark extract has been found to be beneficial for heart failure, coronary artery disease, and high cholesterol levels coronary arterial disease (Subramaniam et al., 2011; Kapoor, 2001). It has been found to significantly increase the activity of lipoprotein lipase as well as plasma lecithin-cholesterol acyltransferase mediated hepatic bile acid synthesis and reduces the activity of lipogenic enzymes including 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), glucose-6-phosphate dehydrogenase and malate dehydrogenase (Patil et al., 2011). The root extracts of *W. somnifera*, *A. calamus*, *R. purpurea* and *G. glabra* have been found to possess significant hypcholesterolemic effect (Bathla et al., 2016; Visavadiya and Narasimhacharya, 2007; Visavadiya and Narasimhacharya, 2006; Parab and Mengi, 2002). Oral administration of the fruit extracts of *T. chebula*, *T. bellirica* and *P. emblica* have been found to cause a significant reduction in serum cholesterol level (Maruthappan and Shree, 2010; Latha and Daisy, 2010; Mathur et al., 1996). The hardwood extract of *A. catechu* exhibited promising anti-dyslipidemic activity (Srivastava et al., 2011). Spikenard possesses significant antiarrrhythmic and hypotensive activities (Disket et al., 2012). Jaggery has been found to significantly reduce the degree of atherosclerosis (Okabe et al., 2009).

Although Mrityunjay possesses significant cardio-protective ingredients, there is a paucity of scientific evidence regarding its cardiac effects. Therefore, considering the significance of the evaluation of safety and efficacy of ayurvedic drugs, therapeutic implication of Mrityunjay in ayurveda and promising cardioprotective properties of its ingredients, the present study was carried out to investigate its cardioprotective effects in an experimental animal model. Cardioprotective effect of the ayurvedic preparation was evaluated by the means of its anti-arrrhythmic (against digoxin-induced arrhythmia) and hypocholesterolemic activities, along with its effect on heart rate, in a rat model.

**MATERIALS AND METHODS**

**Drugs used in the study**

The ayurvedic preparation, Mrityunjay, was procured from Sree Kundeswari Aushadhalaya Ltd., Batch#003, Chittagong, Bangladesh. As described on the manufacturer’s label, each 5 mL of the preparation contains 28.24 mg of the extract of *R. serpentina* root, *T. arjuna* bark, *G. glabra* root, *T. involucrate* whole plant and other ingredients individually according to the Bangladesh National Formulary of ayurvedic Medicine. Ketamine hydrochloride (Gonoshasthaya Pharmaceuticals Limited, Dhaka, Bangladesh) and digoxin (Aristopharma Ltd., Dhaka, Bangladesh) were obtained as gifted samples. Diagnostic kits were purchased from Exim GmbH (Germany) for the measurement of lipid profile.

**Experimental animals**

Twenty healthy Sprague-Dawley albino rats (90-120 g) were obtained from the animal resources center of the Department of Pharmacy, Jahangirnagar University, Savar, Dhaka. The rats were individually housed in stainless steel cages at room temperature and with sufficient ventilation. The rats of either sex were allowed to acclimatize for seven days prior to drug pre-treatment. They were randomly divided into four groups (n = 5). Distilled water was the only source of fluid, along with liquid drug in pre-treated groups. Each group of rats were provided with sufficient fluid and feeds and re-weighed after 35 days of pre-treatment.

**Experiment protocol**

Animals were grouped into four groups containing 5 animals in each group (n = 5). Group one rats was given normal food and water *ad libitum* thrice daily for 35 days. This group of rats was referred to as the control rats. Group two rats were given food and water *ad libitum* thrice daily for 35 days. On the 36th day, digoxin was administered (20 mg/kg b.w., i.p.). This group of rats is referred to as digoxin control rats. Group three rats were given normal food and water *ad libitum* with Mrityunjay low dose (0.28 mL/kg b.w.) orally (p.o.) for 35 days. On the 36th day, digoxin was administered (20 mg/kg b.w., i.p.); this group is referred to as the Mrityunjay low dose pre-treated rats. Group four rats were given normal food and
Electrocardiographic study of Mrityunajay on digoxin-induced arrhythmic rats

The experiment was performed using Edan VET-300 veterinary ECG machine (China). Digoxin arrhythmogenic dose (AD) has been proposed to be 13 ± 1 mg/kg b.w., in adult rats by Weinhouse et al. (1983). This was taken as a reference point to start screening for an arrhythmogenic dose of digoxin for the current studies. Doses of 8, 10, 13, 15, 20 and 22 mg/kg b.w. was administered intraperitoneally in ketamine anesthetized rats and electrocardiogram was monitored continuously for 60 min. Auto (all leads) and rhythm (lead II) was recorded to observe any characteristic arrhythmic changes. A concentration of 20 mg/kg b.w. i.p. was chosen for induction of arrhythmia without causing death for 60 min. Rats were weighed and then anesthetized with ketamine (50 mg/kg b.w., i.p.). After anesthesia, rats were placed on dissecting board filled with wax and pinned to it by small pins. Then electrodes, smeared with electrode gel, were connected to the two forelimbs, two hind limbs, and chest. ECGs recordings were taken for 30 min, after 20 min of ketamine hydrochloride (50 mg/kg b.w., i.p.) injection. The recordings were performed before and 60 min after digoxin (20 mg/kg b.w., i.p.) administration. Arrhythmias were assessed by identifying and quantifying the different changes in heart rate during the 60-min recording period. The ECG was recorded as lead I, II, III, aVR, aVL, aVF and V (chest lead). For this study, only lead II was discussed. A schematic diagram of the experimental process is presented in Figure 1.

Hematological effect of Mrityunajay on digoxin-induced arrhythmic rats

Humatzer 3000 (Blood analyzer, Germany) was used for this experiment. Rats were fasted overnight before collection of blood. After ECG recording, an incision was made into their thoracic cavities.

Blood samples were collected by aorta puncture using 5 mL hypodermic syringe and dispensed into 1.5 mL microcentrifuge Eppendorf tubes. The samples were allowed to stand for 30 min at room temperature to clot. Serum for the assays was thereafter separated from the clot by centrifugation at 4000 rpm for 5 min using a centrifuge machine.

The supernatant, that is serum was harvested by simple aspiration with Pasteur pipette and transferred into another microcentrifuge tube. All the biochemical determinations were carried out immediately after separation of the serum from the clot; the serum samples were not stored. Diagnostic kits for the lipid profile (with the exception of low-density lipoprotein-cholesterol, LDL-C) were used according to the manufacturer’s instruction for the estimation of serum lipid profile. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were estimated spectrophotometrically using the methods described by Friedewald et al. (1972).

Data analysis

Data were expressed as mean ± S.E.M. (n = 5). Differences in mean values between experimental groups were analyzed by two tailed student’s t-test. Differences in mean values between experimental groups were analyzed by one-way ANOVA (analysis of variance) followed by Dunnett’s multiple comparison tests where applicable. A probability value less than 0.05 (p<0.05) was defined to be significant.

RESULTS

Body weight observations

Body weight was taken initially on day one and finally on day 36. The result is shown in Table 1. Pre-treatment of Mrityunajay did not alter body weight compared to control group.
Table 1. Effect of drugs on body weight (gm) after pre-treatment of Mrityunjay.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mL/kg)</th>
<th>Initial weight (g)</th>
<th>Final weight (g)</th>
<th>Body weight gain (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>108.75 ± 4.27</td>
<td>130 ± 2.04</td>
<td>21.25 ± 3.15&lt;sup&gt;ns&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low dose</td>
<td>0.28</td>
<td>100 ± 4.08</td>
<td>125 ± 3.54</td>
<td>25 ± 3.23&lt;sup&gt;ns&lt;/sup&gt;</td>
</tr>
<tr>
<td>High dose</td>
<td>2.8</td>
<td>98.75 ± 3.15</td>
<td>126.25 ± 2.39</td>
<td>27.5 ± 2.5&lt;sup&gt;ns&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SEM (n = 5). ns = not significant; *p<0.05 when compared to control group.

Figure 2. Arrhythmogenic dose (AD) determination by administering varying doses of digoxin (selected tracings: A, 8 mg/kg b.w.; B, 10 mg/kg b.w.; C, 13 mg/kg b.w.; D, 15 mg/kg b.w.; E, 20 mg/kg b.w.; F, 22 mg/kg b.w., i.p.).

Electrocardiographic studies

**Determination of arrhythmogenic dose of digoxin**

The ECG wave forms were analyzed after intraperitoneal administration of digoxin at the doses ranging from 8-22 mg/kg b.w. and have been depicted in Figure 2. The dose 8 mg/kg b.w., i.p. did not produce any changes in heartbeat (Panel A); 10-13 mg/kg b.w. exhibited bradycardia (Panel B-C), 15 mg/kg b.w., i.p. induced unstable atrial fibrillation (Panel D), 20 mg/kg b.w., i.p. caused stable induction of arrhythmia, atrial flutter (AF) (Panel E), and 22 mg/kg b.w., i.p. produced agonal beats or dying beats (Panel F) which was an indication of severe digitalis intoxication. Therefore, the dose 20 mg/kg b.w. i.p. of digoxin was selected to induce arrhythmia without causing the death of animals.

**Induction of arrhythmia by digoxin**

In the whole experiments, the injection of digoxin (20 mg/kg b.w., i.p.) induced atrial fibrillations (AFib) and atrial flutters. It also induced ventricular bigeminy, junctional rhythm (inversed p wave), idioventricular rhythm. Additionally, it showed digitalis effect characterized by ST-sagging. The ECG results are shown in Figure 3.

**Effect of low dose of Mrityunjay on ECG tracings**

Atrial fibrillation, bigeminy rhythm, and digitalis effect were not seen after pre-treatment of 0.28 mL/kg b.w. of Mrityunjay. Mrityunjay only showed atrial fibrillation briefly, which had a delayed onset compared to the
digoxin-control rats. Atrial fibrillation and other rhythm abnormalities were absent in Mrityunjay pre-treated groups (Figure 4).

Effect of high dose of Mrityunjay on ECG tracings

After pre-treatment of Mrityunjay at the dose of 2.8 mL/kg b.w, p.o., atrial fibrillation, atrial flutter, bigeminy rhythm, and digitalis effect were not observed. Mrityunjay showed no abnormal beats but decreased heart rate following digoxin administration (Figure 5).

Effect of Mrityunjay on heart rate

Heart rate (HR) changes before and after administration of digoxin were noted in digoxin control (group II) and
Figure 5. ECG tracings of Mrityunjay (2.8 mL/kg b.w., group IV) showing NSR (A) changes after Digoxin (20 mg/kg b.w., i.p.) administration (B). Panel A showed normal sinus rhythm (NSR), panel B showed sinus bradycardia (SB). The recording speed from panel A, B is 50 mm/s. ECG tracings are chosen from one of the five (n = 5) similar and representative control experiments. NSR, normal sinus rhythm; AFib = atrial fibrillation; AF = atrial flutter.

Figure 6. Effect of Mrityunjay treatment (low dose = 0.28 mL/kg b.w., high dose = 2.8 mL/kg b.w.) on heart rate of rodents before digoxin injection (20 mg/kg b.w., i.p.). Values are presented as mean ± SEM (n = 5). *p<0.05, compared to digoxin control group.

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duration of action of Mrityunjay on ECG

Figure 6 shows the duration of normal sinus rhythm (NSR), sinus bradycardia (SB), atrial fibrillation (AFib), atrial flutter (AF), bigeminy rhythm (BR), junctional rhythm (JR), and digoxin effect (DE) of digoxin which were 8 ± 1.22, 23.5 ± 3.16, 2.25 ± 2.11, 13.5 ± 2.33, 2.75 ± 1.01, 6.5 ± 1.05 and 2.75 ± 1.05 min, respectively. The duration of NSR, SB, AF and JR for Mrityunjay low dose (0.28 mL/kg b.w.) pre-treatment was 7.75 ± 1.03, 43.25 ± 4.11, 3.5 ± 0.22, and 5.5 ± 0.21 min, respectively. Pre-treatment of Mrityunjay with high dose (2.8 mL/kg b.w.) caused 11 ± 2.11, 40.75 ± 4.66, and 8.25 ± 1.18 min of NSR, SB, and JR, whereas, AFib, BR were absent. Mrityunjay pre-treatment induced significantly (p<0.05) SB at both high and low doses compared to digoxin control group. On the other hand, it significantly (p<0.05) reduced AFib, AF and DE at both doses.

Hematological test for serum lipid profile

As depicted in Figure 9, Mrityunjay pre-treatment at a low dose (0.28 mL/kg b.w.) for 35 days did not induce a significant decrease of TC, TG, LDL-C and an increase in the HDL-C level of serum, compared to control group. There was a significant decrease (p<0.05) in serum TC...
and LDL-C with the pre-treatment with a higher dose (2.8 mL/kg b.w.) of Mrityunjay. A higher dose of Mrityunjay did not decrease TG significantly but increased the HDL-C level of serum significantly ($p<0.05$) compared to the control group. The effects of Mrityunjay were dose dependent. In high dose pre-treatment, the decrease in TC, TG, and HDL-C was insignificant where LDL-C was significant ($p<0.05$) compared to the low dose pre-treatment group.

**DISCUSSION**

An insignificant increase in body weight was observed between the Mrityunjay pre-treated groups and the control group by five weeks after initiating oral administration (Table 1). It has been reported that digoxin is 100 times more potent in rodents than humans by the means of therapeutic efficacy and toxicity (Gonano et al., 2011). The dose of digoxin (20 mg/kg b.w., i.p.) has been
selected by trial and error based approach which systematically and reproducibly produced arrhythmias in experimental rats (Figure 2). In addition, this dose of digoxin has been reported to produce low toxicity in the heart of rats (Dutta and Marks, 1972). In control experiments, it was observed that digoxin at an order of magnitude below the dose used, did not promote arrhythmias within the first hour following administration, whereas digoxin at an order of magnitude above the one used, killed the animals during the first few minutes.

Atrial fibrillation, bigeminy rhythm, and digitalis effect were absent in Mrityunjay low dose pre-treated group (Figure 4). Mrityunjay only showed atrial fibrillation briefly, which had a delayed onset compared to the digoxin-control rats. Atrial fibrillation and other rhythm abnormalities were absent in Mrityunjay pre-treated groups. High dose pre-treatment of Mrityunjay did not produce atrial fibrillation, atrial flutter, bigeminy rhythm, and digitalis effect was absent in the group (Figure 5). The pre-treatment showed a decrease in heart rate but no abnormal beats before and after digoxin administration (Figures 6 to 7). Therefore, it can be suggested that Mrityunjay successfully inhibited digoxin-induced arrhythmia at both doses.

Oral pre-treatment of Mrityunjay significantly (p<0.05) as well as completely inhibited atrial fibrillation and bigeminy rhythm (Figure 8) at both high and low dose level. It significantly (p<0.05) delayed onset as well as decreased the duration of atrial flutters. Furthermore, Mrityunjay inhibited reduction of heart rate which was induced by digoxin and stabilized heart rhythm (Figures 7 to 8). The effect could be attributed to the negative chronotropic action of Mrityunjay. However, Mrityunjay showed marked bradycardia following induction of arrhythmia. This is possibly due to the presence of rauwolfia alkaloids in the preparation, which shows bradycardia, particularly when used concurrently with digitalis (Barnhart, 1991). Digoxin inhibits Na⁺/K⁺-ATPase for a prolonged period of time that in turn activates the Na⁺/Ca²⁺ exchanger which increases the intracellular concentration of the Ca²⁺ ion. Ajmaline, an anti-arrhythmic drug, present in R. serpentina may contribute to this effect (Kiesecker et al., 2004).

Lower dose pre-treatment of Mrityunjay did not exhibit significant changes in serum lipid profile of rats (Figure 9). However, chronic pre-treatment of Mrityunjay at a higher dose (2.8 mL/kg b.w., p.o.), significantly (p<0.05) decreased TC and increased in HDL-C level of rat serum. The decrease in TC may be attributed to the presence of rauwolfia alkaloids and possible inhibition of cholesterol biosynthesis by down regulation of HMG-CoA reductase, inhibiting mevalonic acid pathway (Rand and Jurevics, 1977; Lüllmann, 2005). The present study also determined LDL-C/HDL-C and TC/HDL-C ratio of blood serum after Mrityunjay pre-treatment (Table 2). Increased value of these indexes indicates progression to the lower risk of coronary artery diseases (Levy et al., 1984). Oral administration of Mrityunjay increased the ratio between

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**Figure 9.** Effect on lipid profile after chronic pre-treatment with Mrityunjay. Data are presented as mean ± SEM (n = 5).

* p<0.05, compared to control group. #p<0.05, compared to low dose. TC = total cholesterol; TG = triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
HDL-C and TC as well as LDL-C in both doses. The results indicate that Mrityunjay could be effective in lowering the risk of coronary artery diseases.

Conclusion

Cardiovascular diseases are now a major health risk in developing countries, like Bangladesh. Ayurvedic formulations are frequently used in the management of cardiac diseases. Although demand for ayurvedic medicines is increasing gradually, their safety and efficacy are still a major concern. While the active constituents of the majority of these plants are well investigated, the specific active constituents for a particular therapeutic efficacy in the plant-based herbal medicines, formulated with several plant species, are still ill established. The present study revealed that ayurvedic preparation, Mrityunjay has a definite and dose dependent modulatory effect on the heart. It may exert potent cardioprotection when subjected to digoxin-induced arrhythmia. It could also lower triglyceride levels significantly. Therefore, considering the potential bioactivity, this drug can be further screened to rationalize its medicinal use.

Ethical approval

All experiments were performed according to the ethical standards laid down in the Declaration of Helsinki 2013. Animals were handled and treated according to the principles of the Swiss Academy of Medical Sciences and Swiss Academy of Sciences. Animals were euthanized according to the Guidelines for the Euthanasia of Animals: 2013 edition.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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REFERENCES


Table 2. Serum lipid parameters of Mrityunjay.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mL/kg b.w.)</th>
<th>HDL-C/LDL-C</th>
<th>HDL-C/TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>0.81 ± 0.05</td>
<td>0.37 ± 0.01</td>
</tr>
<tr>
<td>Low dose</td>
<td>0.28</td>
<td>0.88 ± 0.02</td>
<td>0.39 ± 0.01</td>
</tr>
<tr>
<td>High dose</td>
<td>2.8</td>
<td>0.93 ± 0.01</td>
<td>0.47 ± 0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM (n = 5). *p<0.05, compared to control group. TC = total cholesterol; TG = triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.


