Research Article

Cardiac Mechanism of Leaves Aqueous Extract of *Cyathula achyranthoides* (Kunth) Moq. (Amaranthaceae) on Rabbit ECG

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ABSTRACT

Objective: *Cyathula achyranthoides* is a pharmacopoeia plant used in traditional medicine to treat heart disease and high blood pressure. According to WHO statistics, approximately 17.9 million deaths worldwide are due to heart disease. This study was carried out to evaluate the effects of an aqueous extract of *Cyathula achyranthoides* (CytiA) leaves on the electrocardiogram of rabbits in the presence of Isoprenalin and Propranolol.

Results: At doses of 1 and 5 mg/kg B.W., CytiA significantly inhibited ($p < 0.001$) the bradycardia-inducing effects of Propranolol. On induced arrhythmia, high doses of CytiA resulted in a significant ($p < 0.001$) reduction in arrhythmia duration of 93.33%, with a Reductive Dose of 50 (RD50) of arrhythmia at 17.37 mg/kg B.W.

Conclusion: *Cyathula achyranthoides* acts via β-adrenergic receptors as a beta-blocker at high doses. On the other hand, low doses act as beta agonists. These results would therefore justify its use in the treatment of heart disease and hypertension.

Keywords: *Cyathula achyranthoides*, electrocardiogram, arrhythmias, beta agonists.

INTRODUCTION

Today in Africa, according to the WHO, 80% of the population rely on traditional medicine for their health needs[1]. As a result, the State of Côte d'Ivoire, in order to make its national health system more dynamic, has created the National Program National of traditional Medicine (NPTM). As part of this program, numerous studies have been carried out on plants used in traditional medicine. Such is the case of *Heliotropium indicum* Linn. (Boraginaceae)[2], and Mimosa invisa (Fabaceae)[3], whose antihypertensive and cardiac effects have been demonstrated.

According to WHO statistics, around 17.9 million deaths worldwide are due to heart disease[4]. Heart disease is therefore a major health problem because of the sudden deaths it can cause.

In our case, we were interested in *Cyathula achyranthoides* (Kunth) Moq. (Amaranthaceae), a plant used in traditional therapy for various diseases including heart disease[5]. Preliminary studies have already been carried out on normal rabbit electrocardiograms. Indeed, the dose-response effect of leaves the aqueous extract of *Cyathula achyranthoides* has shown that low doses lead to an increase in cardiac activity, whereas high doses lead to a decrease in this activity[5].

In the present study, the interaction of low doses with Propranolol and high doses with Isoprenalin was investigated in order to reveal the extract's mechanism.

MATERIALS AND METHODS

MATERIALS

Animal

Rabbits of the species *Oryctolagus (Leporidae)*, all from the same farm in Abidjan in the commune of Cocody with an average weight of 2 kg, were acclimatized at the UFHB Biosciences UFR animal facility for a few days before use [6]. The care and handling of the animals met the ethical requirements for scientific purposes, in accordance with international guidelines on ethics in animal experimentation (DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes) applied to the Biology and Health Laboratory of the Felix HOUPHOUET-BOIGNY University.

Plant material

The plant material used for this study is a medicinal plant of the species *Cyathula achyranthoïdes* (kunth) Moq. (Amaranthaceae). It was harvested at the Felix HOUPHOUET-BOIGNY University in March 2024. It was identified at the National Floristic Center of Felix HOUPHOUET-BOIGNY University by comparison with herbarium number UCJ000014C.

Physiological and pharmacological solutions

This is the reference physiological solution (NaCl 9‰, used for dissolving plant extract and diluting pharmacological substances). Pharmacological substances such as: Thiopental (Neon Laboratories, India) used for animal

anesthesia. Isoprenalin (Monico S.P.A., Italy), a beta agonist, and Heparin (Cheplapharm, Germany), an anticoagulant, and Propranolol (Merckle, Germany), a beta-blocker, were used in this work.

METHODS

Preparation of the aqueous leaf extract of *Cyathula achyranthoides* (Kunth) Moq.

The fresh plant is washed and rinsed twice with distilled water. Next, 731 g of the plant in 4.5 L of distilled water were decocted at 260°C for 45 min.

The resulting decocted was then filtered through a white cloth (poplin), once through N°4 coffee filter paper and finally through absorbent cotton. The filtrate is oven-dried (THERMO SCIENTIFIC VT 6060 MY6, Germany) at 70° for 72 hours. After 72 hours, we obtained the brown-colored dry extract we named CytiA.

Study of the interaction of CytiA and substances on the rabbit electrocardiogram.

Preparation of the Animals

The method used is that of Abo[7]. The rabbit is anesthetized by injection into the lateral marginal vein with thiopental at a concentration of 0.5 g/mL, depending on the animal's body weight. The saphenous vein is catheterized for injection.

The armpits of the two forelimbs and the groin of the two hind limbs of the rabbit are shaved and cleaned with 90° ethyl alcohol. These shaved areas are coated with a conductive gel (Ultrasound gel KONIX, USA) and four electrodes are placed on them.

CytiA - propranolol interaction on rabbit ECG

A single dose of propranolol (Propra) at 50 mg/kg B.W., was prepared and diluted in NaCl 9‰. This dose is post-administered to the animal after the 1 and 5 mg/kg B.W. doses of the extract having positive chronotropic and inotropic effects.

It is injected 10 seconds before the CytiA doses and the recording is made over 1 min30 s to see the effects of the interaction between these two injected substances on the rabbit's electrical cardiac activity.

Interaction of CytiA-Isoprenalin on rabbit ECG

This study is performed according to the modified method of Ayenon [8]. In this experiment, Isoprenalin (Iso) at a dose of 10^{-2} mg/kg B.W. is pre-administered to rabbits 10 seconds before doses of 10, 15, 20 and 30 mg/kg B.W. of aqueous extract inducing negative chronotropic and inotropic effects.

The recording is made over 1 min 30 s to see the interactive effects of the two injected substances on the rabbit's cardiac electrical activity.

Statistical analysis

GraphPad Prism 5.01 software (San Diego, USA) was used for statistical analysis of the results of this study.

Data was analyzed by statistical analysis of variance (ANOVA test), followed by Dunnett's multiple comparison tests. The difference between two values was considered significant if $p < 0.05$.

The results are presented in the form of the mean, together with the error of the mean (M±ESM). This software also enabled us to perform statistical processing of ECG parameters and then construct graphs (curves and diagrams).

RESULTS

Interaction of CytiA and Isoprenalin on rabbit ECG.

Anti-arrhythmic effects of CytiA on P waves, T waves and PR interval

Figure 1 shows the results of the interactive effects of increasing doses of CytiA with a single dose of Isoprenalin (10^{-2} mg/kg B.W.) on the rabbit ECG. Normal ECG values for P waves, T waves and PR interval were 0.17 ± 0.04 mV; 0.21 ± 0.06 mV and 0.072 ± 0.004 s, respectively. Injection of Isoprenalin alone resulted in a significant increase ($p < 0.05$; $p < 0.01$) in P-wave and T-wave amplitude and a significant reduction ($p < 0.001$) in PR interval duration compared with normal recording. The variations in these parameters obtained were 64.70%, 138.09% and 58.33% respectively compared with normal.

When CytiA doses (10; 15; 20; 25 and 30 mg/kg B.W.) are administered after this dose of Iso, there is a significant decrease ($p < 0.05$; $p < 0.01$; $p < 0.001$) in P-wave and T-wave amplitude compared with the effect of the single dose of Isoprenalin. The maximum variations were achieved with the 30 mg/kg B.W. dose, and were 46.42%, 70% and 13.66% respectively, compared with the effect of Isoprenalin alone.

The variations observed in these ECG parameters are shown in **Table 1.**

Anti-arrhythmic effects of CytiA on heart rate.

Normal (control) ECG rate is 220 ± 5.4 bpm. When the single dose of Iso is injected, there is a significant ($p<0.001$) increase in heart rate of 50% compared with normal.

After the single dose of Iso, doses of 10, 15, 20, 25 and 30 mg/kg B.W. of CytiA injected, resulted in a significant ($p<0.05$; $p<0.01$; $p<0.001$) decrease in heart rate compared to the effect of Iso alone.

Thus, the maximum reduction of 90.90% is obtained with the 30 mg/kg B.W. dose.

The diagram in **Figure 2** shows the variations obtained.

Anti-arrhythmic effect of CytiA on the QRS complex

The diagrams in figure 3 show the different variations in the amplitude of the QRS complex in this experiment.

Injection of the Iso dose alone results in a significant increase ($p < 0.001$) in QRS amplitude compared with the normal recording of 0.48 mV. Injection of Iso alone resulted in a 78% increase in QRS amplitude.

When CytiA doses of 20, 25 and 30 mg/kg B.W. are injected after Iso, the amplitude of the QRS complex decreases significantly ($p < 0.05$; $p < 0.01$ and $p < 0.001$) compared with the effect of Isoprenalin alone. The maximum reduction in this Iso-induced increase is 83.33% and is achieved with the 30 mg/kg B.W. dose.

III.4.4. Anti-arrhythmic effect of CytiA on the duration of Iso-induced arrhythmia.

A single Iso dose of 10-2 mg/kg B.W. induces an arrhythmia lasting 75 s. When CytiA doses of 10, 15, 20, 25 and 30 mg/kg B.W. of CytiA are injected, arrhythmia duration is significantly reduced from 65 s to 5 s.

At 30 mg/kg B.W., there was a 93.33% reduction in Iso-induced arrhythmia duration. The CytiA Reducing Dose (DR50) of 50% of arrhythmia duration is 17.37 mg/kg B.W.

Figure 4 shows the percentage reduction in arrhythmia duration as a function of CytiA dose.

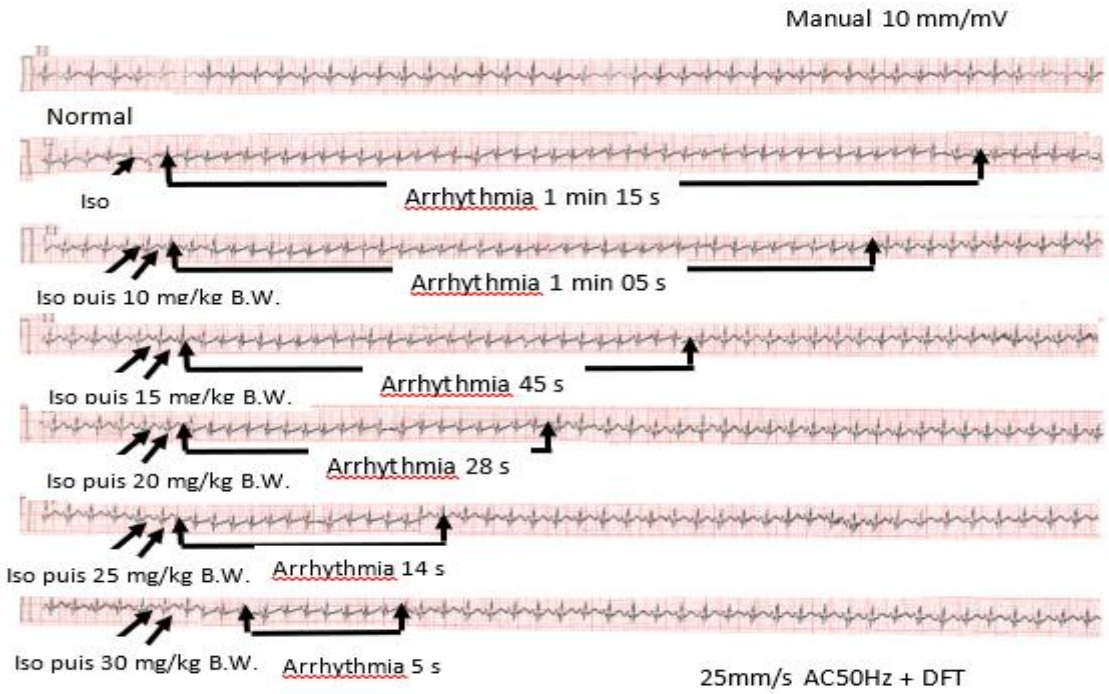

Figure 1: Effect of the aqueous extract of *Cyathula Achyranthoides* (KUNTH) MOQ on an arrhythmia induced by Iso.

Table 1: Value of the different parameters of ECG of an arrhythmia induced by Isoprenaline in pre-administration then treated with the CytiA

Dose	P-Wave (mV)	T-Wave (mV)	PR Interval (s)
Normal	0.17 ± 0.04	0.21 ± 0.06	0.072± 0.004
Isop. 10^{-2} mg/kg B.W.	0.28 ± 0.07 **	0.5 ± 0.05*	0.03 ± 0.003***
Isop. 10^{-2} mg/kg B.W. before 10 mg/kg B.W. of ext.	0.23 ± 0.06	0 .42 ± 0.07	0.044 ± 0.004
Isop. 10^{-2} mg/kg B.W. before 15 mg/kg B.W. of ext.	0.2 ± 0.07	0.3 ± 0.06	0.052 ± 0.005
Isop. 10^{-2} mg/kg B.W. before 20 mg/kg B.W. of ext.	0.19 ± 0.06*$_1$	0,24 ± 0,05	0.060 ± 0.005*$_1$
Isop. 10^{-2} mg/kg B.W. before 25 mg/kg B.W. of ext.	0.17 ± 0.05*$_1$	0.19 ± 0.06*$_1$	0.68 ± 0.006**$_1$
Isop. 10^{-2} mg/kg B.W before 30 mg/kg B.W. of ext.	0.15 ± 0.06**$_1$	0.15 ± 0.05**$_1$	0.071 ± 0.004***$_1$

n=3

**: p<0.05; **: p<0.01; ***: p<0.001 significant compared to normal recording*

**1: p<0.05; **1: p<0.01; ***1: p<0.001 significant compared to the effect of Iso alone*

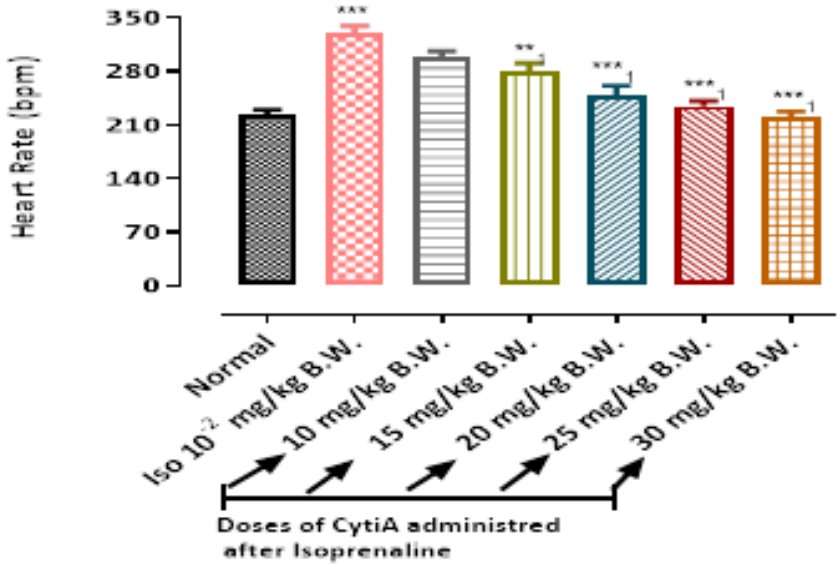

Figure 2: Heart rate (bpm) plot versus CytiA doses administered after the Isoprenalin.
n=3
***: P<0.01; compared to normal electrocardiogram*
***1: P<0.001; ***1: compared to the effect of isoprenalin*

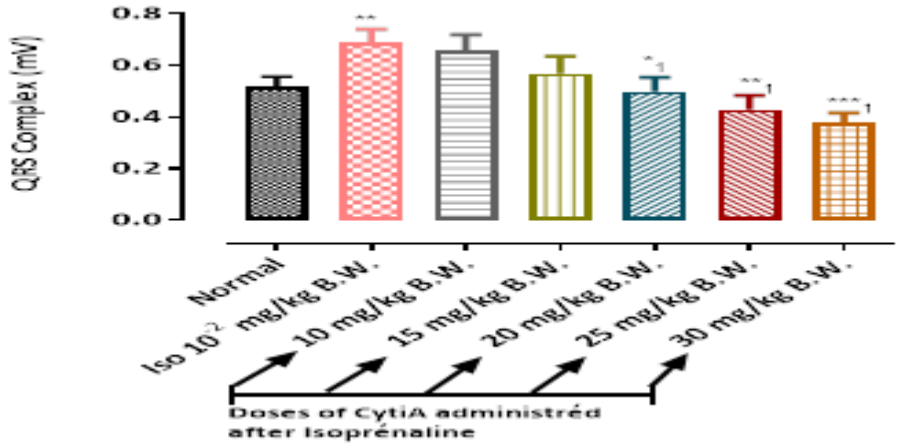

Figure 3: Diagram of variation in the amplitude of the QRS complex as a function of the doses of CytiA administered after the dose of Isoprenalin.
n = 3
***: p <0.01; Compared to the normal electrocardiogram*
1: p <0.05; ** 1: p <0.001; * 1: in relation to the effect of isoprenalin*

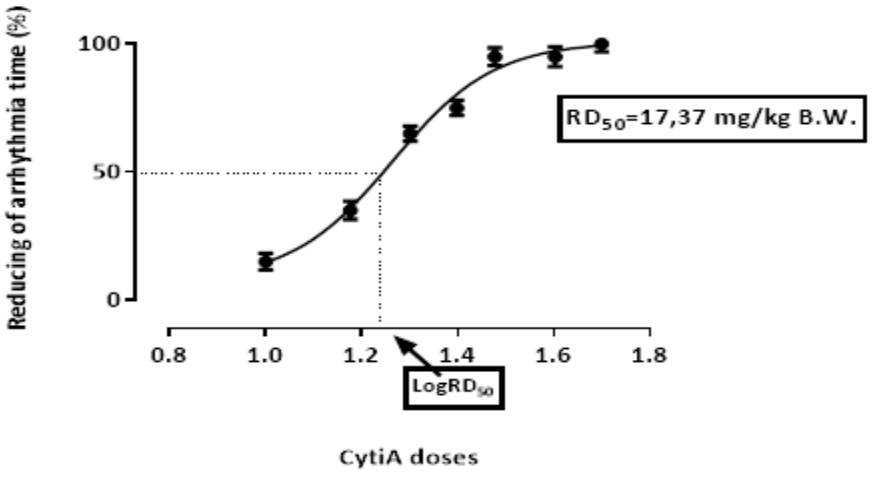

Figure 4: Curve to reduce the duration of the arrhythmia induced by Iso. In pre-administration (%) as a function of DR_{50} logarithm ($LogDR_{50}$).

Interaction of aqueous CytiA extract with propranolol

Effect of Propra-CytiA interaction on P and T waves and PR interval.

In this study, extract doses of 1 and 5 mg/kg B.P. were injected prior to a propranolol dose of 50 mg/ kg B.W. The normal ECG of this series of experiments gives us the following P and T wave and PR interval values: 0.18 ± 0.06 mV; 0.03 ± 0.002 mV and 0.056±0.003 s.

Injection of a single dose of Propra 50 mg/kg B.W. alone resulted in a significant ($p < 0.001$) decrease in P-wave and T-wave amplitude and a significant ($p < 0.001$) lengthening of the PR interval compared with normal recording. The variations obtained were 38.88%, 66.66% and 78.57% respectively.

On the other hand, the amplitude of P and T waves increased significantly ($p < 0.05$; $p < 0.01$) following administration of 1 and 5 mg/kg B.W. of CytiA before Propra, compared with the effect of Propra alone. The maximum variations were obtained with 5 mg/kg B.W. and were 81.81% and 30% respectively.

As for the PR interval, its duration was significantly reduced ($p < 0.01$) when CytiA doses of 1 and 5 mg/kg B.W. were administered before Propra, compared with the effect of Propra alone. It is reduced by 50% compared with the effect of Propra alone.

Figure 5 shows a typical recording obtained following interaction with propranolol and CytiA extract, and the values are recorded in **Table 2**.

Effect of Propra-CytiA interaction on heart rate (bpm).

The diagram in Figure 6 shows the effects of Propra-CytiA interaction on heart rate.

The normal heart rate in this study is 240 ± 6.6 bpm. When Propra was administered to the animal, there was a significant ($p < 0.01$) decrease of 20.83%.

Post-administration of a single dose of Propra. 50 mg/kg B.W. after doses of 1 and 5 mg/kg B.P., gives a significant increase ($p < 0.05$; $p < 0.01$) in heart rate compared with the effect of propranolol alone. The increase is 80% for 5 mg/kg B.W. of CytiA.

Effect of Propra-CytiA interaction on QRS complex (mV)

In this series of experiments, the QRS complex amplitude of the normal recording is 0.42 ± 0.09 mV.

When Propra is injected alone, the amplitude of the QRS complex decreases significantly ($p<0.01$) by 30.95%, compared with the normal recording.
However, when Propra is injected after CytiA doses of 1 and 5 mg/kg B.W., there is a significant increase ($p<0.05$; $p<0.01$) in QRS complex amplitude compared with the effect of Propra alone. The dose of 5 mg/kg B.W. thus resulted in an 84.61% increase over the effect of Propra alone.
The diagram in **Figure 7** shows the effect of Propra interaction and CytiA doses of 1 and 5 mg/kg B.W. on the QRS complex.

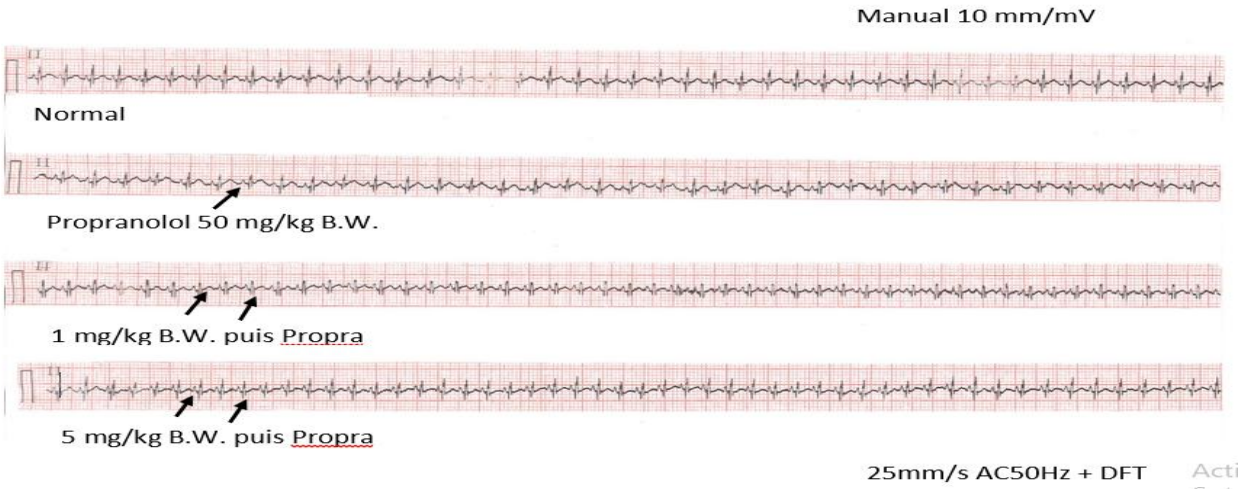

Figure 5: Interaction of the aqueous extract of *Cyathula achyranthoides* (kunth) Moq. (CytiA) with propranolol on rabbit ECG.

Table 2: ECG parameter values following the interaction between Propranolol and CytiA.

Dose	P-Wave (mv)	T-Wave (mv)	PR Interval (ms)
Normal	0.18±0,06	0.03±0.002	0.056±0.003
Propanol 50 mg/kg B.W.	0.11±0.06**	0,05±0.003*	0.1±0.03**
CytiA 1 mg/kg B.W. before 50 mg/kg B.W. of Propra	0.18±0.07**$_1$	0.03±0.004*$_1$	0.05±0.003**$_1$
CytiA 5 mg/kg B.W. before 50 mg/kg B.W. of Propra	0.2±0.08**$_1$	0.035±0.03*$_1$	0.05±0.003**$_1$

n = 3
**: p <0.05; **: P <0.01 significant compared to normal recording*
**1: p <0.05; ** 1: P <0.01 significant compared to the Iso effect alone*

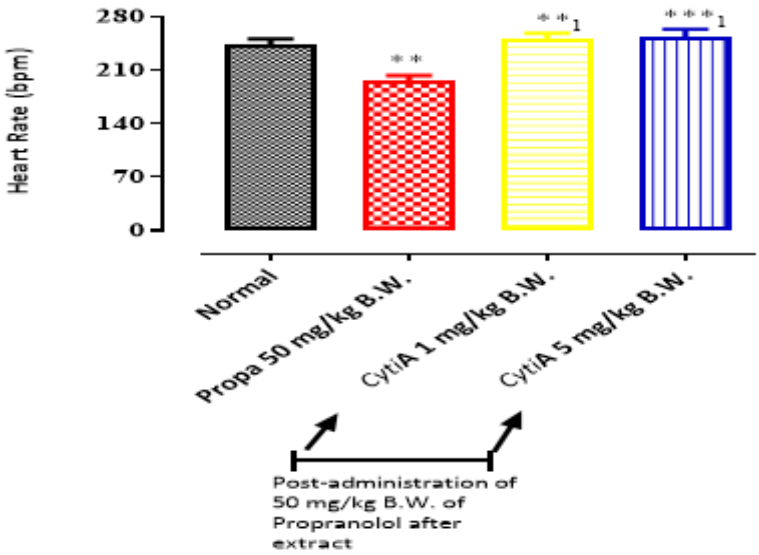

Figure 6: Heart frequency diagram as a function of the post-administration of 50 mg/kg B.W. of Propra. after the doses of the CytiA.
n = 3
**: Compared to normal ECG.*
**1; ** 1: in relation to the effect of the propra.*

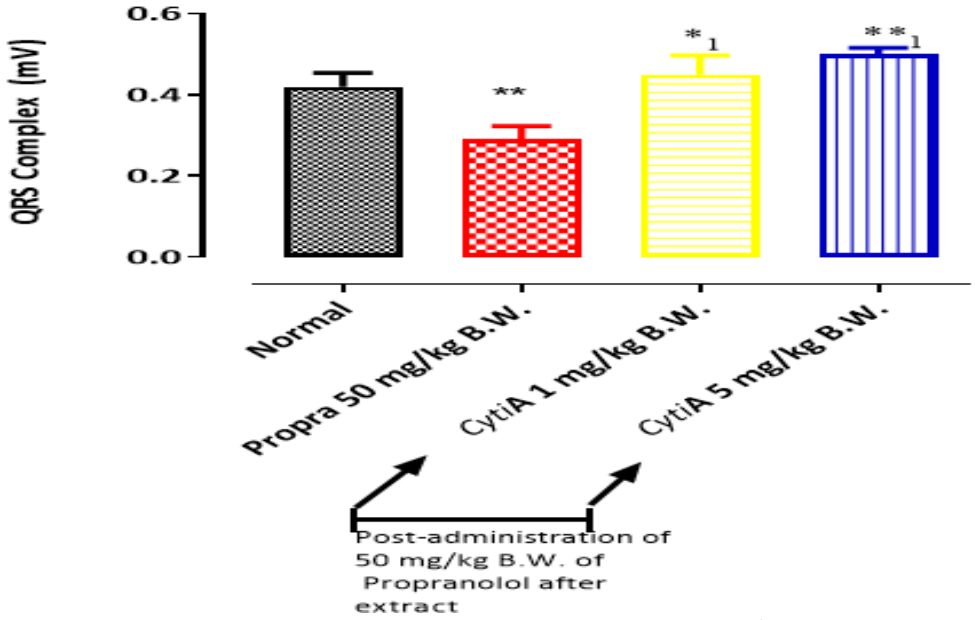

Figure 7: QRS complex amplitude plot as a function of post-administration of 50 mg/kg B.W. Propra after doses of CytiA aqueous extract.
n=3
***: Compared to normal ECG.*
**1; **1: Compared to the effect of Propra.*

DISCUSSION

This study was conducted at two levels, for high doses interacting with Isoprenalin and for low doses interacting with propranolol.

In the first instance, the interaction was carried out with the single dose of Isoprenalin 10^{-2} mg/kg B.W. Indeed, Isoprenalin (a sympathomimetic agent) is often used experimentally or clinically to induce atrial fibrillation[9]. Similarly, Isoprenalin acts on beta-adrenergic receptors in the heart, increasing heart rate and the force of contraction of cardiac muscle[10]. Isoprenalin is a beta-1 agonist which increases atrioventricular conduction velocity and myocardial contractile force by lowering the myocardial excitability threshold. Isoprenalin also induces tachycardia with arrhythmia, often of the ventricular type[11]. In our case, the amplitudes of the P wave and QRS complex decrease, while the heart rate of rabbits increases, when they receive a dose of Isoprenalin. Our results are in line with those of Ayenon[8]. Indeed, according to his work, increasing doses of

Isoprenalin led to a reduction in the amplitude of P, T and QRS waves and an increase in heart rate with the onset of atrial fibrillation for a dose of 0.1 µg/kg B.W. Isoprenalin[8].

Injection of the single dose of Isoprenalin resulted in a 75-second arrhythmia. Following the Isoprenalin-induced tachycardia and arrhythmia, injection of high doses of CytiA significantly ($p<0.001$) reduced the Isoprenalin-induced arrhythmic effect. This shows that, at these doses, the extract either opposes β1-adrenergic receptor activation. The extract would therefore contain beta-blockers. Beta-blockers reduce heart rate (negative chronotropic effect), myocardial contractility (negative inotropic effect), cardiac output and atrioventricular conduction velocity (negative dromotropic effect) [12-13]. These drugs reduce the force of contraction of the heart (negative inotropic effect) [14]. Like beta-blockers, CytiA may also reduce the transmission of nerve impulses to the heart. Finally, according to Camm[15], arrhythmia suppression by beta-blockers is common.

Secondly, at low doses such as 1 and 5 mg/kg B.W., we realized an interaction with propranolol. Indeed, propranolol is a non-selective beta-adrenergic blocking agent (β1 and β2), which means that it decreases basal beta-receptor activity[16]. CytiA doses of 1 and 5 mg/kg B.W. negate the negative inotropic and chronotropic effects of propranolol. At low doses, the β1 agonists and/or sympathomimetic substances contained in the extract may have predominant effects. At these doses, the aqueous extract of *Cyathula achyranthoides* leaves would activate beta-adrenergic receptors by acting as a β1 agonist. Indeed, β1 agonists are cardioselective and therefore act specifically on the heart to induce positive inotropic and chronotropic effects[17-18]. In contrast, propranolol acts both on the heart, maintaining the effect of the extract even in the presence of propranolol.

CONCLUSION

The present study was carried out using leaves aqueous extract of *Cyathula achyranthoides* (kunth) Moq. (CytiA) to evaluate its effect on induced cardiac arrhythmia in rabbits.

Similarly, at low doses, the extract reduced propranolol-induced bradycardia, and at high doses, it reduced Isoprenalin-induced arrhythmia. By having this dual effect, CytiA would therefore be highly beneficial for different types of arrhythmia.

The various results obtained in this study clearly indicate the reasons for using this plant in traditional medicine to treat heart disease.

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