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(RESEARCH ARTICLE)

CARDIOTONIC ACTIVITY OF AN AQUEOUS LEAF EXTRACT OF *EUPHORBIA SUDANICA* (EUPHORBIACEAE) IN AN ISOLATED FROG'S HEART MODEL

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ABSTRACT

Objective: The present study was to analyse the cardiotonic effect of the aqueous leaf extract of *Euphorbia sudanica* (Euphorbiaceae) on the contractility of the isolated frog's heart and to determine a likely mechanism of action.

Material and methods: Preliminary phytochemical screening was carried out on the aqueous leaf extract of *Euphorbia sudanica*, then the frog's heart was isolated and perfused with various substances using the Langerdhorff device for measuring the cardiac contractility parameters. Frog ringer was used as a vehicle for administration of the extract and digoxin as well as adrenaline served as the standards. The qualitative phytochemical screening revealed the presence of reputed cardiotonic compounds such as glycosides and flavonoids.

Results: The results obtained also showed that the aqueous leaf extract of *E. sudanica* (1 mg / mL) significantly induces positive inotropic (74.07%) and chronotropic (18.29%) effects on the isolated frog's heart, respectively manifested by increased of force of contraction and heart rate, compared to hearts perfused with normal ringer. However, in the presence of propranolol (β-adrenergic antagonist) and amlodipine (calcium channel blocker), adrenaline and aqueous leaf extract of *Euphorbia sudanica* did not increase heart rate, force of contraction or cardiac output, because those parameters did not differ significantly from control. This led to suggest that the aqueous leaf extract of *Euphorbia sudanica* might cause increased calcium ion influx as a result of their action on β-adrenergic receptors, at the concentrations used.

Conclusion: The aqueous leaf extract of *E. sudanica* showed a strong cardiotonic effect that is likely to be mediated through β-adrenergic receptors. The given biological activity is due to chemical content of this plant extract.

Keywords: *Euphorbia sudanica*, Frog heart, Inotropic effect, Chronotropic effect.

1 INTRODUCTION

Cardiovascular diseases affect, as the name suggests, the heart and all the blood vessels that run throughout the body and the brain. They occupy a prevalent place in terms of hospitalization worldwide and constitute the main cause of human mortality [1, 2]. Many cardiotonic drugs are used in the treatment of cardiovascular diseases, some with positive inotropic effects such as cardiac glycosides, other adrenergic and dopaminergic receptor agonists and finally calcium mobilizers and phosphodiesterase inhibitors [3]. Despite their therapeutic efficacy, their inaccessibility, their intoxication and their narrow therapeutic margins in the clinic remain relevant [4]. Hence, there is a need to explore other means of treatment. The plant trail is often used to provide patients with a wider range of solutions [5]. Many plants have already been subjected to study of cardiotonic activity, but several remain without scientific and experimental evidences justifying their traditional use [6, 7]. The plant *Euphorbia sudanica*, which is often found in rocky areas and occasionally in botanical gardens in Sub-Saharan Africa, possesses antioxidant properties that can disrupt cardiac function.[8]. Glycosides, flavonoids, polyphenols, and alkaloids all of which are thought to have antioxidant and cardiotonic properties are among the chemical substances found in the aqueous leaf extract of *E. sudanica,* according to preliminary screening of phytochemicals.

Furthermore, the leaves of *Euphorbia sudanica* are used as poison in Africa, and some authors mention in the literature that they may interferes with cardiac mechanics [9, 10]. Experimental verification of the cardiotonic potential of this plant would allow us to promote it in the treatment of heart failure.

2 MATERIAL AND METHODS

2.1 Standard drug

Digoxin and adrenaline

2.2 Animal

All experimental interventions involving frog (*Bufo bufo)* specimens were executed in rigorous compliance with the National Institutes of Health directives governing the housing, handling, and ethical treatment of research fauna (NIH Publication No. 85-23, 1985 revision).

2.3 Composition of physiological solution

Ringer's solution for amphibian was used as a physiological solution to maintain the rhythm of the isolated tissue. The composition of Ringer's solution in 1 L of distilled water was as follows: NaCl (9 g/L), KCl (0.42 g / L), $CaCl_2$ (0.24 g / L), dextrose (1.0 g / L) and $NaHCO_3$ (0.5 g / L).

2.4 Equipment

Kymograph (Orchid Scientific, model SRD-01) and Starling's lever were used to record cardiac contractility parameters. Test drug: Aqueous leaf extract of *Euphorbia sudanica*

2.5 Plant material and Preparation of extract

The plant material was harvested in the city of Roua, Soulédé-Roua sub-division, Department of Mayo Tsanaga, Region of the Far-North-Cameroon and its taxonomic identification was made by comparison with a recorded sample under number 58647/HNC at the National Herbarium of Yaoundé. A quantity of 50 g of the pulverized botanical substrate was

combined with 450 mL of distilled water and subjected to thermal extraction at 70 °C for 60 min. Following ambient cooling, the suspension was clarified by vacuum-assisted filtration through Whatman GF/C grade 4 membrane filters (90 mm diameter). The resulting liquid phase was concentrated under reduced pressure in a forced-air desiccator maintained at 45 °C until a viscous, chestnut-colored concentrate was obtained. This semi-solid residue constituted the aqueous phyto-extract employed in all subsequent experimental procedures.

2.6 Preliminary phytochemical test

Preliminary phytochemical testing was done on the aqueous leaf extract of *E. sudanica* using standard laboratory methods [11].

2.7 Experimental Protocol

2.7.1 Preparation of isolated frog's heart

Thirty adult frogs of both sexes (body weight: 40–65 g) were utilized for this study. Animals were maintained in a controlled aquatic enclosure at the Maroua Protestant College and provided *ad libitum* access to a standard diet throughout the acclimatization period. Isolated heart preparations were established following a well-established amphibian cardiac protocol. Briefly, frogs were humanely euthanized via double pithing (cranial and spinal) to abolish central nervous reflexes, then secured in a supine position on a dissecting tray. The thoracic cavity was opened by carefully excising the ventral integument, sternum, and associated musculature to expose the pericardial sac, which was subsequently incised to visualize the heart. A fine incision was made in the sinus venous, through which a cannula pre-filled with amphibian Ringer's solution was gently advanced in a retrograde direction into the ventricular chamber. The cannula was secured with a silk ligature around the vascular base while gently elevating the ventricular apex to ensure stable fixation. Finally, the heart was carefully dissected free from adjacent connective tissues and transferred to the perfusion apparatus for experimental recording. [12].

2.7.2 Method of recording cardiac contractility parameters

The Langerdhorff type device was used to measure the heart contractility characteristics. In fact, the Starling lever was attached to the heart, and the necessary modifications were made to record the heart's reactions. By fastening a glass tube in the cap to the reservoir (Marriott bottle), the Ringer solution level in the Syme cannula was kept constant. Before an infusion containing test medicines was administered, the isolated heart was cleaned with Ringer's solution for approximately five minutes until a standard cardiogram was recorded on a kymograph paper wrapped around a spinning drum operated by a motor at a speed of 1.25 mm/s. Prior to infusion with each medication concentration, the heart was cleaned with Ringer's solution [9], and the cardiac contractility characteristics were noted.

2.8 Evaluation of cardiotonic potential

The cardiotonic activity of digoxin and an aqueous leaf extract of *E. sudanica* was evaluated using isolated frog heart preparations. Heart rate (HR), contractile force amplitude (FC), and cardiac output (CO) were recorded to quantify dose-dependent responses following sequential administration of the reference compound or test extract. After each treatment, tissues were rinsed with Ringer's solution for approximately 2 min to restore baseline physiological parameters. Digoxin was tested at concentrations of 0.125, 0.25, and 0.5 mg/mL. Recovery of spontaneous rhythmic contractions was confirmed post-wash. Preparations that failed to maintain regular contractility were promptly replaced with fresh specimens to ensure experimental consistency. The aqueous leaf extract of *E. sudanica* was prepared at 0.5, 1, and 2 mg/mL. Baseline contractile activity was recorded following tissue equilibration in Ringer's solution. Preparations that exhibited loss of regular rhythmic beating were promptly replaced with fresh isolated hearts to ensure consistent experimental conditions.

2.9 Exploration of potential mediation pathways

2.9.1 Adrenergic pathway

Once the baseline contractile activity was recorded, adrenaline was administrated at 10^{-2} mg/ml. After 4 minutes, this was followed by propranolol (10^{-4} mg/mL) or aqueous leaf extract of *E. sudanica's* (3 mg/mL) infusion.

2.9.2 Calcium channels

Isolated frog heart preparations were perfused with either adrenaline (1×10^{-2} mg/mL) or an aqueous leaf extract of *E. sudanica* (3 mg/mL), following injection with amlodipine (1×10^{-6} mg/mL).

2.9.3 Cholinergic pathway

To compare the cardiotonic activity of the extracts used with the one of cholinergic antagonists, the hearts isolated from the frogs were perfused with the aqueous leaf extract of *E. sudanica* at a concentration of 1 mg/mL preceded by atropine for 4 minutes.

2.10 Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM) from six independent replicates (n = 6). Statistical analyses were performed using GraphPad Prism software version 5.0 (GraphPad Software, San Diego, CA, USA). Following verification of variance homogeneity, one-way analysis of variance (ANOVA) was applied, and intergroup comparisons of means were conducted using Tukey's post hoc test. A p-value < 0.05 was considered statistically significant.

3 RESULTS

3.1 Qualitative phytochemical analysis of aqueous leaf extract of *E. sudanica*

The results of the qualitative phytochemical analysis of the aqueous leaf extract of *E. sudanica* revealed the presence of glycosides, alkaloids, steroids, tannins, polyphenols, terpenoids and flavonoids.

3.2 Evaluation of the cardiotonic potential of the aqueous leaf extract of *E. sudanica*

Perfusion of the hearts with the aqueous leaf extract of *E. sudanica* (1mg / mL) resulted in a significant increase ($p < 0.001$) of 18.29%, 59.09% and 78.82% for heart rate (HR), force of contraction (FC) and cardiac output (CO). On the other hand, digoxin perfusion in frog's heart (0.5 mg / mL) caused a significant decrease ($p < 0.05$) of about 31.43% in the HR, and significant increase ($p < 0.05$) of about 51.15 % in the FC, compared to the normal control (Figure 1). Not with standing this increase, there is a reversible cardiac arrest at a concentration of 5 mg / mL because after rinsing the heart almost regains its normal contractility (Figure 2).

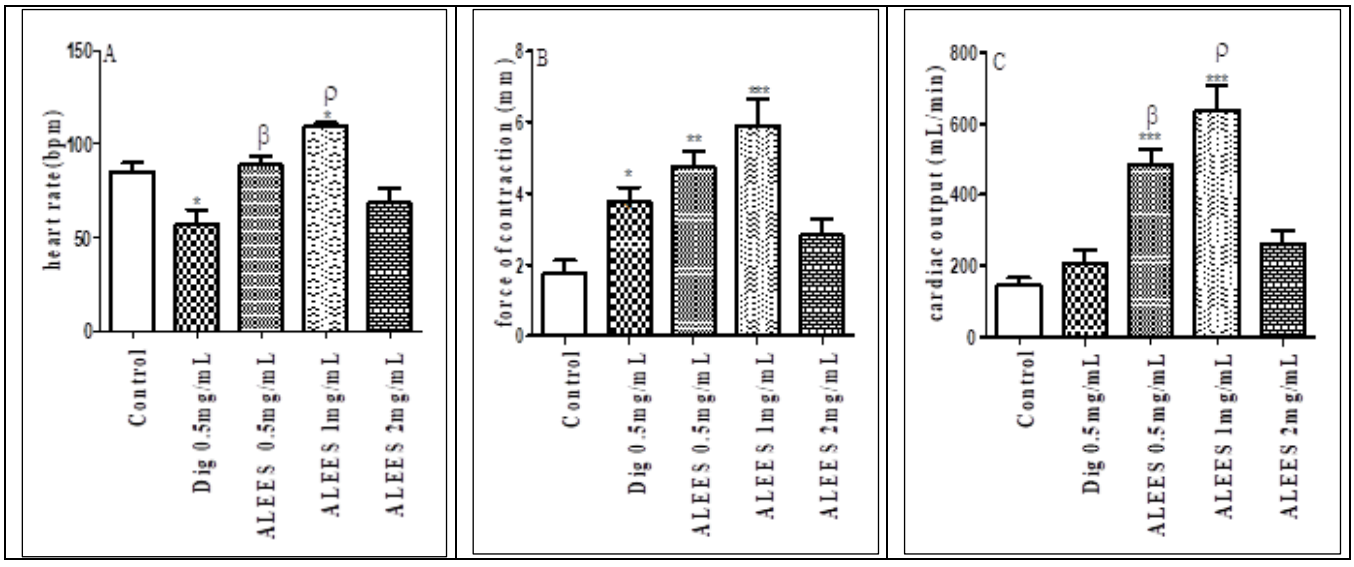


Figure 1: Effect of aqueous leaf extract of E. sudanica on heart rate (A), force of contraction (B) and cardiac output (C) of isolated frogs' hearts. Each value represents the mean. SEM, n = 6.

*** P <0.001; ** P <0.01, * P <0.05: significant difference compared to the control; βp <0.01; ρp <0.001: significant difference compared to digoxin. Dig: digoxin; ALEES: aqueous leaf extract of Euphorbia sudanica.

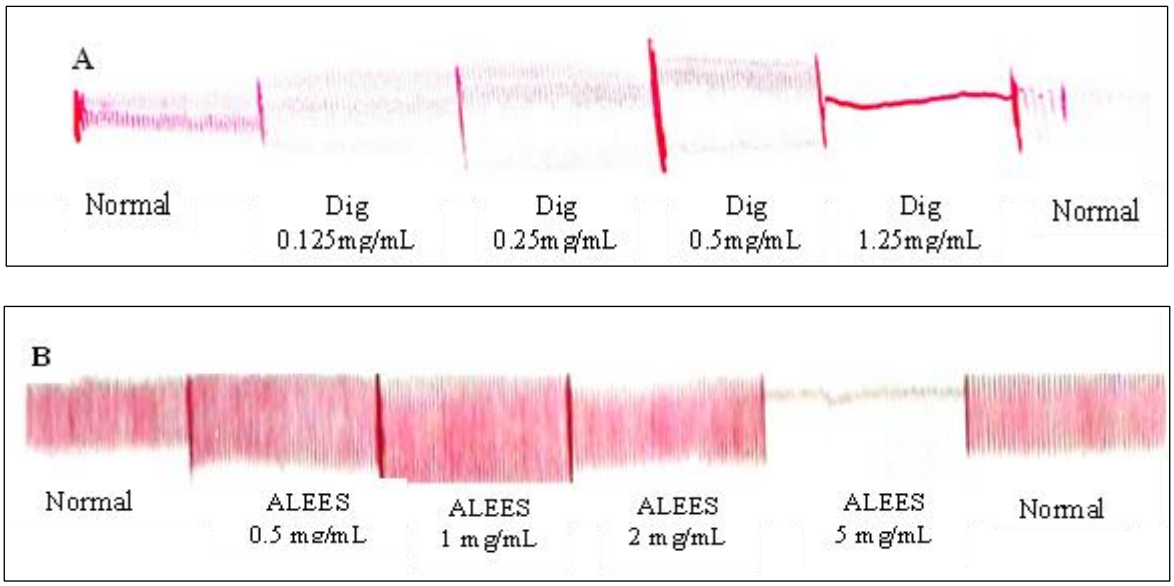


Figure 2: Recording showing the cardiotonic activity of digoxin (A) and of the aqueous leaf extract of E. sudanica (B) on the functioning of the isolated frog heart. Dig: digoxin; ALEES: aqueous leaf extract of Euphorbia sudanica.

3.3 Exploration of potential mediation pathways

3.3.1 Adrenergic pathway

Figure 3 shows the interaction of adrenaline or the aqueous leaf extract *of E. sudanica* with the adrenergic blocker (propranolol). When compared to normal ringer, perfusion of adrenaline caused a significant increase ($p<0.05$) of 54.08%, 52.12% and 61.82% in heart rate, force of contraction and cardiac output respectively. Perfusion of aqueous leaf extract *of E. sudanica* of the order of caused an increase of 17.97%, 79.60% and 64.45% in heart rate, force of contraction and cardiac output respectively. When propranolol is administered before extract or adrenaline, there is a significant decrease ($p<0.001$) in cardiac contractility parameters compared to the normal control (Adr). The decrease was about 40.07%; 79.59% and 77.37% for adrenaline and 46.81%; 79.60% and 89.14% for the aqueous leaf extract of *E sudanica* (Figure 4).

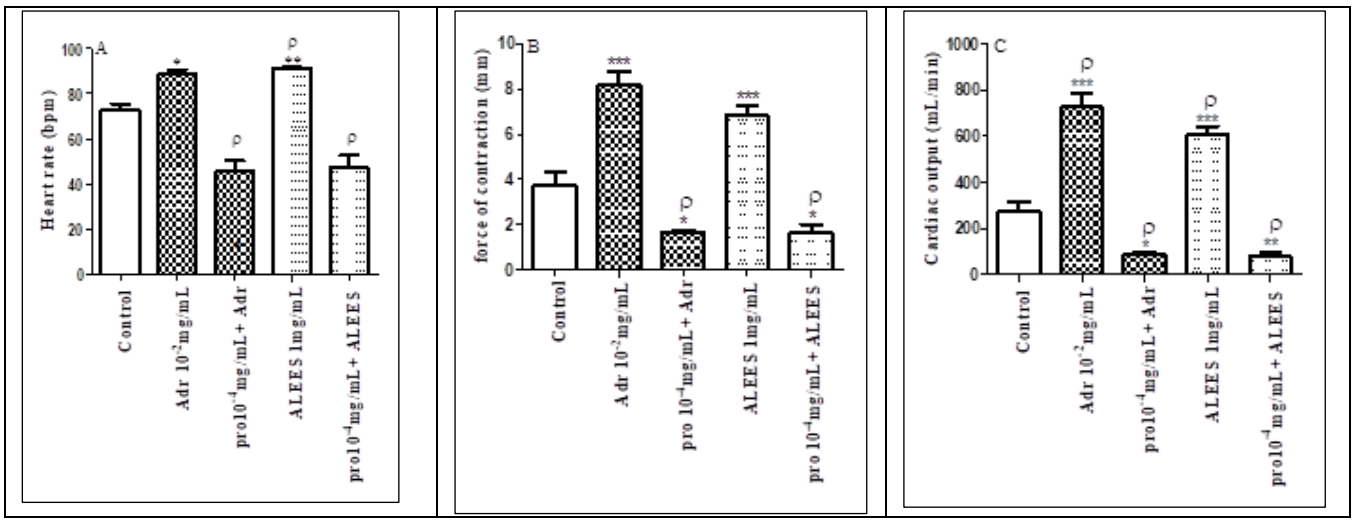


Figure 3: Effect of propranolol (pro) ; Adrenaline, and aqueous leaf extract of E. sudanica on heart rate (A), force of contraction (B) and cardiac output (C). Each value represents the mean SEM, n = 6.

*** P <0.001; ** P <0.01; * P <0.05: significant difference compared to the control; ρp <0.001: significant difference from adrenaline. Adr: adrenaline ; Pro: propranolol; ALEES: aqueous leaf extract of Euphorbia sudanica.

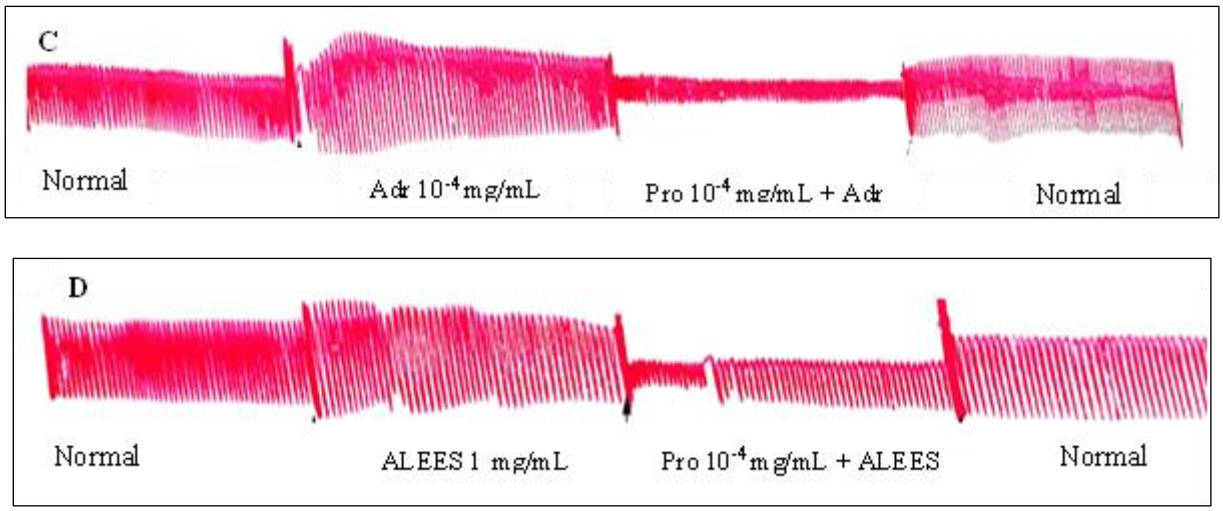


Figure 4: Recording showing the impact of propranolol (1×10^{-4} mg/mL) on adrenaline (C) and the aqueous leaf extract of E. sudanica (D) on the functioning of the isolated frog heart.

Adr: adrenaline; Pro: propranolol; ALEES: aqueous leaf extract of Euphorbia sudanica.

3.3.2 Calcium channels

As illustrated in figure 5 that, hearts perfused with adrenaline and those perfused with the aqueous leaf extract of *E. sudanica* showed a significant increase ($p<0.05$) in contractility parameters. This increase was about 18.68%; 54.08% for HR, FC and CO respectively with adrenaline and 17.77%; 42.30 and 52.08 for HR, FC and CO with aqueous leaf extract of *E. sudanica*, compared to the normal control. However, a significant decrease in these parameters is noted compared to the normal control and positive control (adrenaline).

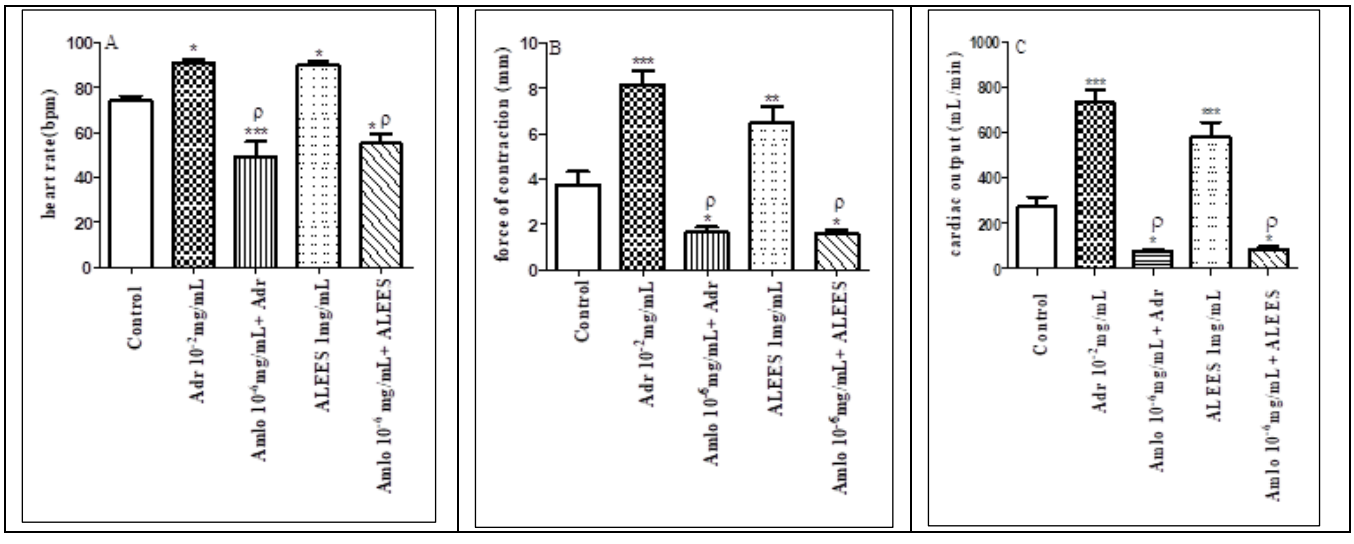


Figure 5: Effect of Amlodipine ; adrenaline , and aqueous leaf extract of E. sudanica on heart rate (A), force of contraction (B) and cardiac output (C). Each value represents the mean ESM, n=6.

**P<0.001; **P<0.01; *P<0.05: significant difference compared to control; ρp< 0.001: significant difference compared to adrenaline. Adr: adrenaline; Amlo: amlodipine ; ALEES: aqueous leaf extract of Euphorbia sudanica.

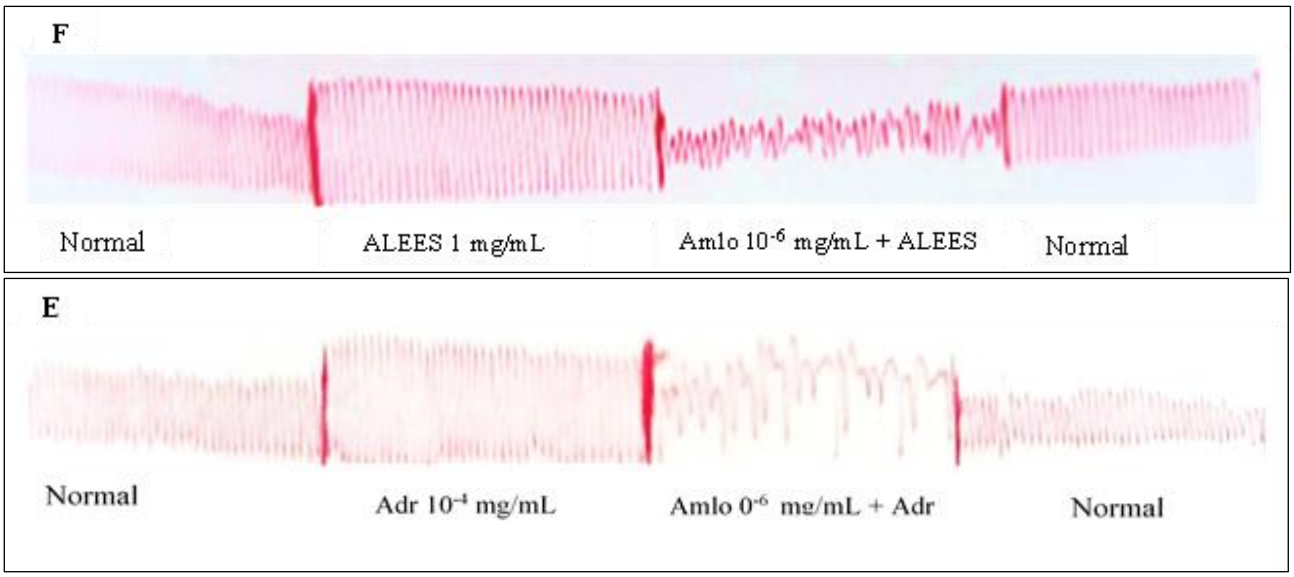


Figure 6: Recording showing the impact of amlodipine (1×10^{-6} mg/mL) on adrenaline (E) and aqueous leaf extract of E. sudanica (F) on the functioning of the isolated frog heart.

Adr: adrenaline; Amlo: amlodipine ; ALEES: aqueous leaf extract of Euphorbia sudanica.

3.3.3 Cholinergic pathway

The results in Figure 7 showed the influence of atropine 0.1mg/kg on the heart contraction parameters generated by acetylcholine and the aqueous leaf extract of *E. sudanica.* When compared to hearts perfused with a normal ringer, hearts perfused with acetylcholine led to a significant decrease ($p<0.01$) in HR, FC and CO by 55.24 %; 33.82% and 54.16% respectively. However, perfusion of hearts with the aqueous leaf extract of *E. sudanica* (1mg/mL) led to a significant increase ($p<0.01$; $p<0.05$) in cardiac contractility parameters. Hearts perfused with atropine alone or in combination with acetylcholine or to the aqueous leaf extract of *E. sudanica* (1mg/mL) showed a significant increase ($p<0.001$) compared to hearts perfused with acetylcholine (10^{-6} M). With regard to the heart rate, likewise, a significant increase ($p<0.001$) in the FC is observed in the order of 82.35% for the aqueous leaf extract of *E. sudanica* alone and 83.56 % when the extract is combined with atropine.

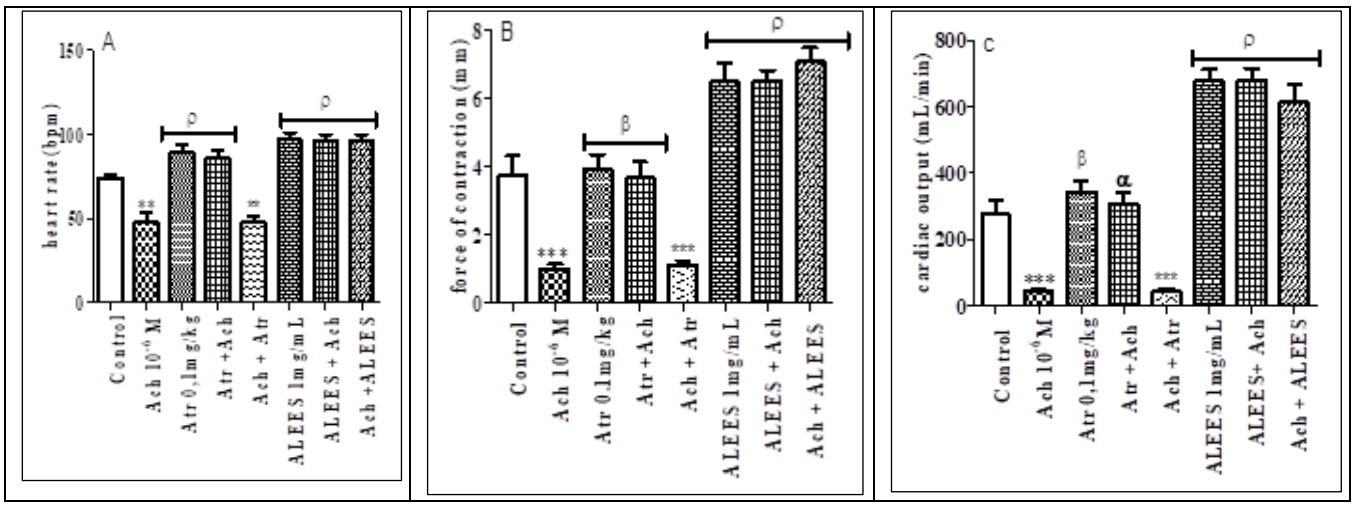


Figure 7: Effects of 10^{-6} M acetylcholine, 0.1 mg/kg atropine, Ach+Atr, 1 mg/mL aqueous leaf extract of *E. sudanica* (ALEES), and ALEES + Atr (0.1 mg/kg) on heart rate (A), force of contraction (B) and cardiac output (C). Each value represents the mean ESM, n=6.

***P<0.001; **P<0.01; *P<0.05: significant difference from control; αp<0.05; βp<0.01; ρp< 0.001: significant difference compared to adrenaline.
Ach: acetylcholine ; Atr: atropine ; ALEES: aqueous leaf extract of Euphorbia sudanica.

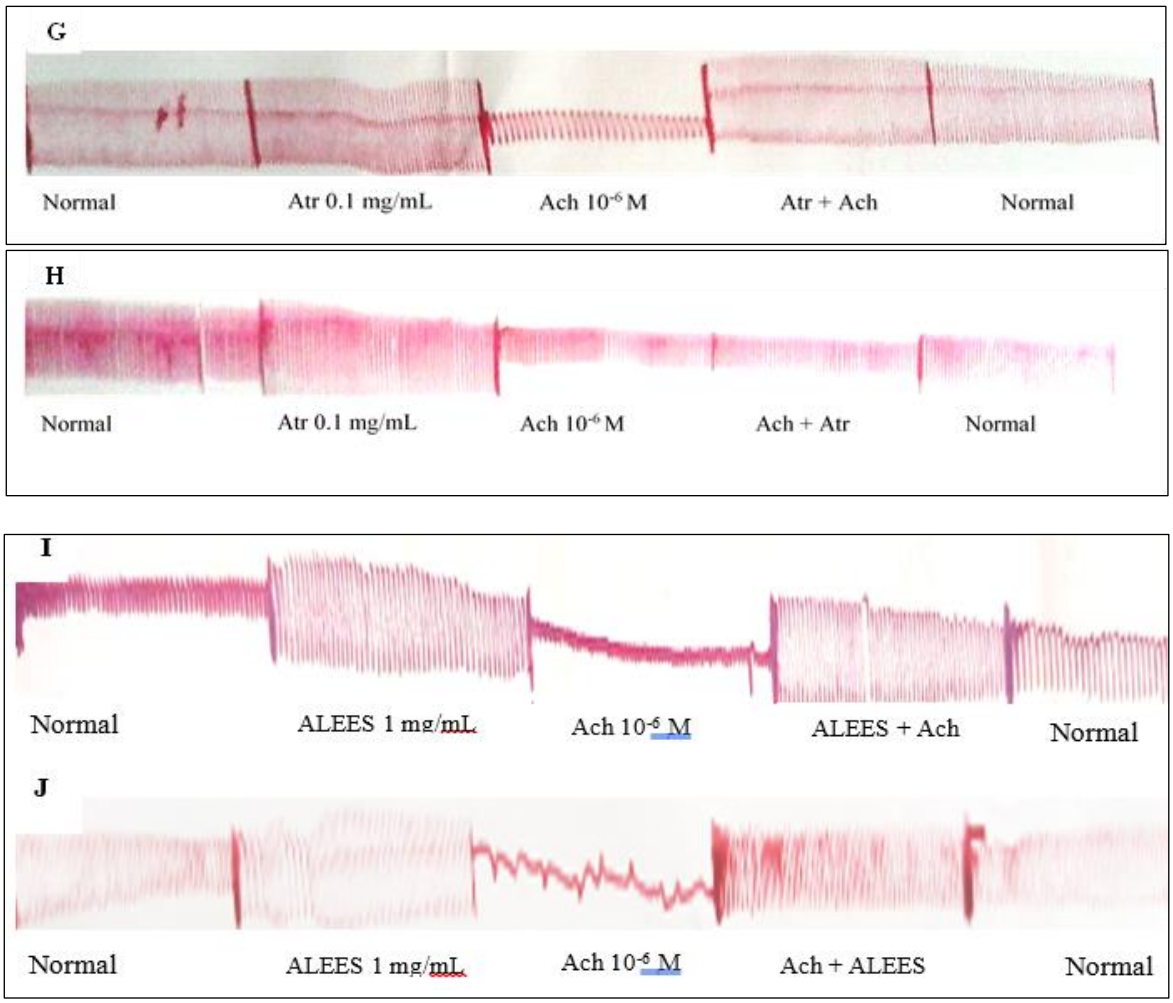


Figure 8: Recording showing the impact of Acetylcholine (10^{-6} M) on Atropine(G, H) and aqueous leaf extract of E. sudanica (I, J) on the functioning of the isolated frog heart.

Atr: atropine; Ach: acetylcholine ; ALEES: aqueous leaf extract of Euphorbia sudanica.

4 DISCUSSION

Different parts of *Euphorbia sudanica* (Euphorbiaceae) are used in traditional medicine for various diseases. The present study was designed to test the cardiotonic activity of the aqueous leaf extract of *Euphorbia sudanica*. The study compare the activity of the plant extract with that of different standard drugs (digoxin and adrenaline) in isolated frogs' hearts under ventricular perfusion. Preliminary phytochemical screening of aqueous leaf extract of *E. sudanica* has revealed the presence of chemical compounds belonging to various families such as glycosides, flavonoids, polyphenols and alkaloids. The compounds found in the aqueous leaf extract of *E. sudanica* used in this study are bioactive substances whose therapeutic potential makes it possible to predict cardiotonic activity. Regarding cardiotonic activity, such as digoxin (tonicardial molecule), the aqueous leaf extract of *E. sudanica* induced a positive inotropic effect at the low concentrations (0.5 and 1 mg / mL) with a more pronounced effect at the concentration of 1 mg / mL. The positive inotropic effect observed is due to the presence of bioactive substances such as glycosides and cardiotonic steroids in our extract. It is known that, glycosides act by blocking the Na^+ / K^+ ATPase pumps causing an increase in the intracellular sodium concentration, which would cause a slowdown, or even a reversal of the Na^+/Ca^{2+} exchanger, responsible for an increase in concentration of Ca^{2+} within the cytosol [13, 14]. Increasing the intracellular Ca^{2+} concentration would activate the contractile elements of the myocardium and smooth vascular fibers that cause the positive inotropic effect [15, 16]. Likewise, there is also a positive chronotropic effect at the concentration of 1mg / mL of our extract. Moreover, It has been previously reported that flavonoids and phenolic compounds are potent antioxidants and are believed to prevent cardiovascular diseases and exhibit a wide range of cardiovascular effects [17]. The aqueous leaf extract of *E. sudanica* (1mg / mL), as well as adrenaline, induces a positive chronotropic and inotropic effect on the isolated frog heart. These activities would be due to the presence of bioactive components such as glycosides and cardiotonic steroids in the extracts [18]. It is known that adrenaline acts on the β1-adrenergic receptors of the heart with corollary the influx of calcium ions due to the opening of slow-type calcium channels . The entry of calcium ions into the myocardial cell triggers the release of calcium from the sarcoplasmic reticulum, which is required

for the activation of the contractile proteins that cause positive inotropic and chronotropic effects [19]. The observed inotropism and chronotropism is thought to be due to the presence of chemical compounds such as glycosides and flavonoids known to be cardiotonic [20, 21]. The chronotropic and inotropic effect can be achieved either by cardiac stimulation or by increasing the intracellular calcium concentration in the cardiomyocytes or by various mechanisms [22, 23]. Propranolol, a β-adrenergic receptor antagonist, showed inhibition of cardiac activity induced by the extract and adrenaline, witch sufficiently explains the existence sympathomimetic agents in the aqueous leaf extract of *E. sudanica*. It is known that adrenaline acts on the β1-adrenergic receptors of the heart with corollary the influx of calcium ions due to the opening of slow-type calcium channels [24]. The entry of calcium ions into the myocardial cell triggers the release of calcium from the sarcoplasmic reticulum, which is required for the activation of the contractile proteins that cause positive inotropic and chronotropic effects [19]. When exposed to propranolol, there is inhibition effect of the aqueous leaf extract of *E. sudanica* as well as adrenaline. Indeed, the works done by Boyer in 2004 and Han in 2016 showed that propranolol of 10^{-4} mg / mL possesses β-blocking properties and opposes the positive inotropic and chronotropic effects induced by adrenaline. This suggests the presence of β-adrenergic substances such as adrenaline in our extract. Likewise, in the presence of amlodipine (calcium blocker), these inotropic and chronotropic effects are seen to be blocked [25]. The contraction of the cardiac muscles is triggered by the reaching of calcium in cell cytoplasm, via specific ion channels on the membrane [26]. Amlodipine selectively inhibits slow-acting membrane calcium channels, preventing the extracellular calcium from entering into cell, it is a calcium channel antagonist [27]. The present study shows that the positive inotropic and chronotropic effect occurs either by stimulation of β receptors or through the opening of slow-acting membrane calcium channels.

5 CONCLUSION

The aqueous leaf extract of *E. sudanica* showed a strong cardiotonic effect that is likely to be mediated through β-adrenergic receptors. The given biological activity is due to chemical content of this plant extract. However further studies are needed to identify the active compound and confirm this mechanism of action.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare that they have no competing interest.

Statement of ethical approval

Prior authorization for the use of animals in this study was obtained from the National Ethics Committee of Cameroon (Reg. N. FWA-IRB 00001954).

The experiments on rats in this study were carried out in accordance with the European Convention for Protection of Vertebrate Animals used for Experimental and other Purposes.

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