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HYDROCOTYLE BONARIENSIS LEAF EXTRACTS: THEIR INFLUENCE ON RABBIT HEMODYNAMICS AND CARDIAC ACTIVITY DYNAMICS

[1]Aissatou F. Kone and [2]Jean-Claude M. Agbénou
[1]Laboratory of Physiology-Pharmacology, Faculty of Sciences, University of Lomé, Togo and [2]Laboratory of Pharmacology and Toxicology, Faculty of Health Sciences, University of Lomé, Lomé, Togo.

Abstract: *Cardiovascular disease (CVD) remains a significant contributor to global mortality, with 17.9 million deaths reported in 2019, accounting for nearly one-third of all global mortalities. Alarmingly, the burden of CVD disproportionately affects low- and middle-income nations, where over three-quarters of CVD-related deaths occur, with 82% of these fatalities transpiring prematurely before the age of 70 (WHO, 2017). Within the West African region, the prevalence of CVD varies widely, ranging from 12% to 69%, highlighting the urgent need for targeted interventions (Kearney et al., 2005; WHO, 2005). Hypertension, a major risk factor for CVD, stands as a prevalent and pressing concern, significantly contributing to the burden of disease. For instance, in Togo, hypertension prevalence reached 36.7% in 2012 within the commune of Lomé (Yayehd et al., 2013). Moreover, despite advancements in modern medicine, traditional remedies remain the primary form of healthcare for approximately 80% of the population in Africa and Asia, emphasizing the importance of understanding and integrating traditional practices within healthcare systems to address the complex challenges posed by CVD.*

Keywords: *Cardiovascular disease, hypertension, prevalence, traditional medicine, low- and middle-income countries.*

INTRODUCTION

Cardiovascular disease (CVD) is now highly responsible for mortality globally. It resulted in 17.9 million mortalities or almost one in three mortalities globally in 2019. Above three-quarters of CVD mortalities and 82% of early mortalities prior to 70 years happen in low- and middle-income nations (WHO, 2017). In West Africa, prevalence ranges from 12% to 69% (Kearney et al., 2005; WHO,2005). Highly prevalent and a major risk factor for cardiovascular disease (CVD), hypertension (hypertension) is at the forefront of these diseases. In Togo, the prevalence of hight blood pressure was 36.7% in 2012 in the commune of Lomé (Yayehd et al., 2013). In Africa and Asia, 80% of the population continues to use traditional rather than modern drugs for primary health care.

These populations use medicinal plants as first-line treatment for various ailments. There is very little evaluation of these treatments, both in terms of frequency of use and benefit/risk ratio for the populations (Fyhrquist et al., 2006). It should be noted that natural products play a predominant role in the discovery of new drugs. They therefore constitute a non-negligible source of potential remedies to combat the development of various forms of resistance to current treatments (Koehn and Carter, 2005).

Hydrocotyle bonariensis Comm. ex-Lam. is a healing plant of the family of Araliaceae greatly appreciated in the local management of numerous diseases in Africa. It is an herbaceous perennial and hairless plant, with numerous horizontal and creeping stems rooting at the nodes. It grows preferentially in large sandy and gravelly riparian areas. It is used by local Togolese doctors to cure diabetes and hypertension. It is utilized as a tranquiller, for fighting liver and kidney issues, tuberculosis, rheumatoid polyarthritis and other diseases (Monyn et al., 2016). Some pharmacological research has shown that this plant has anti-inflammatory and antioxidant activities (Masoumian et al., 2011). But the evaluation of its antihypertensive properties has not yet been the subject of scientific studies. Given the impact of hypertension, the main risk factor for CVD on the health of populations, we have set ourselves the objective of evaluating the antihypertensive properties of the hydro-ethanolic leaf extract of *H. bonariensis*. Specifically, the extract's impacts will be analyzed on blood pressure and cardiac activity in rabbits. The hypotensive effect of this extract will then be compared to the hypotensive effects of a calcium channel blocker, a beta-blocker, and a diuretic, reference molecules used in treating hypertension. The interest of this comparative research is to determine the relative efficiency level of *H. bonariensis* extract compared to these reference molecules in order to arrive at a natural medicine with very few side effects based on this plant.

MATERIALS AND METHODS

Plant material

Hydrocotyle bonariensis (Araliacea) leaves were harvested at the test station of the Higher School of Agronomy of the University of Lomé and identified at the Laboratory of Botany and Plant Ecology of the Faculty of Sciences. Here, the sample was placed under the number " TG 15183". Tap water was used to wash the leaf sample and then air conditioner was used to dry it at 20°C.

Preparation of the hydro-ethanol extract

After the *Hydrocotyle bonariensis* (Araliacea) leaves were dried for 3 weeks, they were sprayed with 320 grams soaked for 72 h. They were shaken intermittently in a hydro-ethanol solvent in an equal volume ratio (1:1). After being macerated, the solution was sieved on filter paper and cotton. A rotavapor was used to evaporate the filtrate under vacuum at 45°C. This yielded 68.28 grams (21.34%) of extract, which was left in a cool environment to prepare the different concentrations utilized for the experiments.

Animal material

48 rabbits (males and females of the species *Oryctolagus cuniculus*, weighing between 1 kg and 1.5 kg) were used for the study. These rabbits come from a breeding farm in the North-West of Lomé specialized in supplying laboratory animals. They were acclimatized for fourteen days in the animal house of the Physiology-pharmacology laboratory of the University of Lomé in order to regulate and

harmonize their physiological state before the experiments. This work followed the ethics of laboratory animal care based on the institutional guidelines and ethics of Laboratory of Physiology/Pharmacology of University of Lome-Togo (ref: 001/2012/ CB-FDS-UL). The work has been approved by the bioethics unit of this laboratory.

Pharmacological tools

The reference substances used are propranolol hydrochloride, a non-selective β-blocker from Sigma Chemical Company;

Nicardipine Chorydrate (Sigma Aldrich) which is a calcium channel blocker; Furosemide (a loop diuretic) from Supelco in France and Heparin, an anticoagulant obtained from Sigma Aldrich, France.

Test of the extract on blood pressure in rabbits and Electrocardiogram (ECG) in rats

Animals' *preparation*

For the study of blood pressure, the rabbit is anesthetized with urethane 80% (1.5 g/kg, i.v.) at 1 ml/100 g body weight rate (Kadissoli et al., 2012). A thin polyethylene catheter connected to a syringe was used to expose and intubate the femoral vein and the carotid artery, as described by Titrikou et al. (2008). The 10% heparinized Ringer's solution was injected at a rate of 0.1 ml/100 g body weight through the femoral vein to prevent blood clotting. A pressure transducer attached to an acquisition system was used to measure the pressure (Power Lab; AD Instruments, Castle Hill, NSW, Australia). The transducer was coupled to a computer mounted with LabChart 6.0 software (AD Instruments**).** To record the electrocardiogram, the rabbit was anesthetized and fixed to the restraint table. A thin polyethylene catheter coupled to a syringe was used to expose and intubate the femoral vein. The 10% heparinized Ringer's solution was inserted at 0.1 ml/100 g body weight rate for preventing blood coagulation. Alcohol was used to shave and clean the armpit of the anterior limbs and groin of the posterior limbs. Four electrodes were connected to these areas in accordance with the colour/location association as specified in the instructions for the recording system (Bleu et al., 2020). An electrocardiogram transducer connected to an acquisition system (PowerLab; ADInstruments, Castle Hill, NSW, Australia) was used to measure ECG. The electrocardiogram transducer was connected to a computer installed with the LabChart6.0 software (AD Instruments).

Administration of products to animals

All products were administered to the rabbits through their femoral vein at a dose of 0.1 ml/100 g, after stabilizing their blood pressure at almost 30 min. The effects of these products on MBP, SBP, DBP and ECG are recorded continuously throughout the experiment.

Dose-response effects of H. bonariensis hydro-ethanol extract on blood pressure and ECG

For blood pressure as for ECG recording, the rabbits were each given Ringer i.v. physiological solution for control and hydroethanolic extract of H. bonariensis leaves at 10, 20, 40, 80 and 160 mg/kg i.v. respectively. Doses below 10 mg/kg are not considered because they have almost no effect.

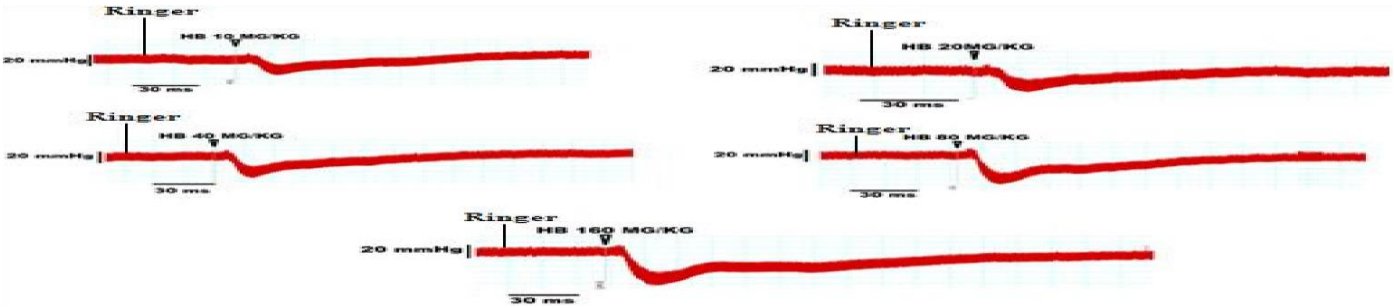

Figure 1. Impact of the hydroethanolic leaf extract of H. bonariensis (10, 20, 40, 80 and 160 mg/kg of body weight) on the rabbit's blood pressure.

Comparison of the effects of propranolol, nicardipine and furosemide with the hydro-ethanolic leaf extract of H. bonariensis

Rabbits are prepared as described in the above protocol for blood pressure measurement in rabbits. They are divided into two groups of three batches (4 batches for the first group) of four rabbits per group. Each lot of the first group had received hydroethanolic extract of *H. bonariensis* leaves (40 mg/kg, i.v.), propranolol (1 mg/kg, i.v.), nicardipine (0.1 mg/kg, i.v.) and furosemide (1 mg/kg, i.v.) respectively. The three lots of the second group received respectively the extract (40 mg/kg, i.v.) + propranolol (1 mg/kg, i.v.); the extract (40 mg/kg, i.v.) + nicardipine (0.1 mg/kg, i.v.); the extract (40 mg/kg, i.v.) + furosemide (1 mg/kg, i.v.). For the treatment of this second group, the products are injected first and then the extract of *H. bonariensis* was administrated immediately.

Statistical analyses

Results are presented as mean ± standard error on the mean. GraphPad Prism 7.0 software was used to process the results, which was also used to build the histograms. Variance analysis was done and then multiple comparison tests (dunnetts'test and kruskal-wallis test). The results are significant if the p-value < 0.05.

RESULTS

Impacts of the hydro-ethanolic extract of *H. bonariensis* on the mean, systolic and diastolic arterial pressure of in rabbits

Figures 1 and 2 show that the hydro-ethanolic leaf extract of *H. bonariensis* caused important decreases of Mean Arterial Pressure (MAP) as the administered dose increased, after almost 10 s of its administration. This decrease of the MAP is 42.73% at the dose of 160 mg/kg in comparison to the control. This extract caused (at the same doses) a less important decrease in Systolic Arterial Pressure (SAP) than the MAP (decrease of 40.39% at 160 mg/kg relative to the control). But the decrease of Diastolic Arterial Pressure (DAP) caused by the extract is relatively greater than that of MAP and SAP at the same doses. Thus, at 160 mg/kg dose, the decrease of the DAP is 50.16% compared to the control. The physiological solution of Ringer, i.v. does not modify either MAP, SAP or DAP. So the extract decrease significantly the MAP, SAP and DAP in rabbits

Impacts of *H. bonariensis* leaf extract on the regulation times of MAP

The time after which MAP returns to basal pressure following the injection of the different doses of hydroethanol extracts of *H. bonariensis* increases proportionally to the dose. This time is respectively 76.34; 80.11; 140.20; 180.13 ($p<0.05$) and 240.23 seconds ($p<0.01$) (Figure 3). The extract effect on MAP continued
according to the administered dose

Effects of *H. bonariensis* on mean arterial pressure in presence of propranolol, nicardipine and furosemide in rabbits

On the first hand, Figures 4 and 5 show the impacts of hydro-ethanolic leaf extract of *H. bonariensis* (40 mg/kg, i.v), propranolol (mg/kg; i.v), nicardipine (0.1 mg/kg; iv) and furosemide (1 mg/kg; iv) on mean arterial pressure in rabbits. It appears from those figures that all these substances cause a decrease in MAP within a range of 29 to 38%. The difference between the effects of the extract and those of the three reference molecules used is insignificant.

On the other hand, Figure 6 shows that the regulation time of MAP (90.40 seconds for the extract alone; 102.36 seconds for the extract + propranolol and 52 seconds for irreversibly and does not return to baseline pressure after injection. There is therefore insignificant variance between the hypotensive effects of the extract compared to the reference drugs. Figure 7 shows the effects of H bonariensis leaves extracts on rabbit's ECG.

Figure 8 shows that the hydro-ethanolic leaf extract of H. bonariensis at 80 and 160 mg/kg BW, i. v causes a significantly decrease in the amplitude of the P-wave (by 28.23 and 28.73% respectively) and QRS wave (by 5.23 and 11.72% respectively).

Figure 9 shows a decrease in heart rate (27.36 and 33.08% respectively). The extract also caused a decrease in the period of the RR interval of 28.23% and 28.73%, respectively. As for the QT, QRS and PR intervals, the extract did not cause any variations. The extract thus causes a decrease in the overall electrical activity of the heart in rabbits.

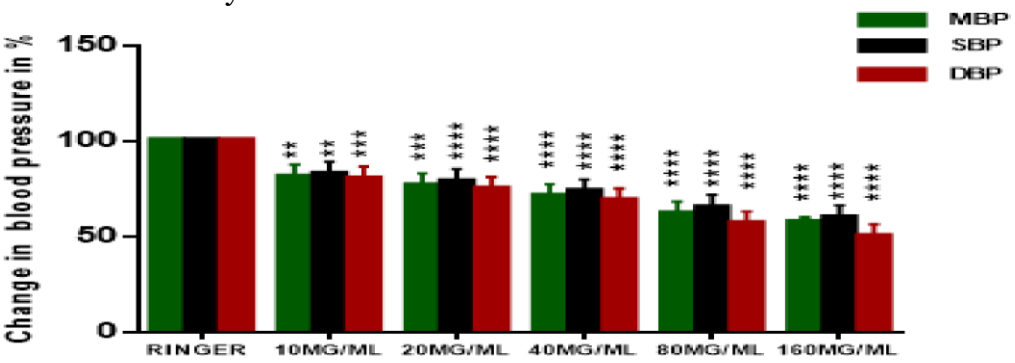

Figure 2. Impacts of hydroethanolic leaf extract of *H. bonariensis* on mean blood pressure (MBP), systolic pressure (SAP) and diastolic pressure (DAP) in rabbits. n = 4; *$p<0.05$; **$p < 0.01$; ***$p < 0.001$ and ****p<0;0001 (ANOVA two ways + Dunnett test). The extract significantly decreased the mean, systolic and diastolic blood pressure, with a much greater variation in diastolic pressure. This decreased blood pressure is important at all doses, from 10 mg/kg.

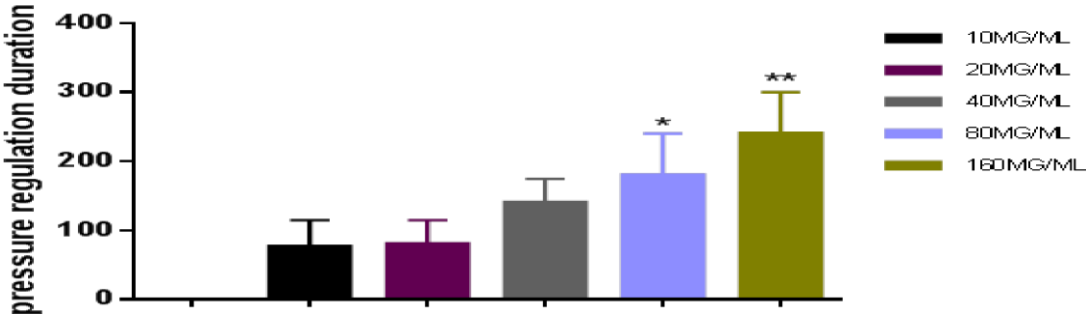

Figure 3. Impacts of hydroethanolic leaf extract of *H. bonariensis* on Mean Blood Pressure (MBP) Regulation times (MBP) in rabbits. n = 4 *p<0.05 and **p < 0.01 (ANOVA one way + kruskal-wallis test). The time to return to baseline pressure after administration of the extract becomes increasingly important as the dose of extract increases. This dose-dependent increase in extract is significant at 80 mg/kg and 160
mg/kg.

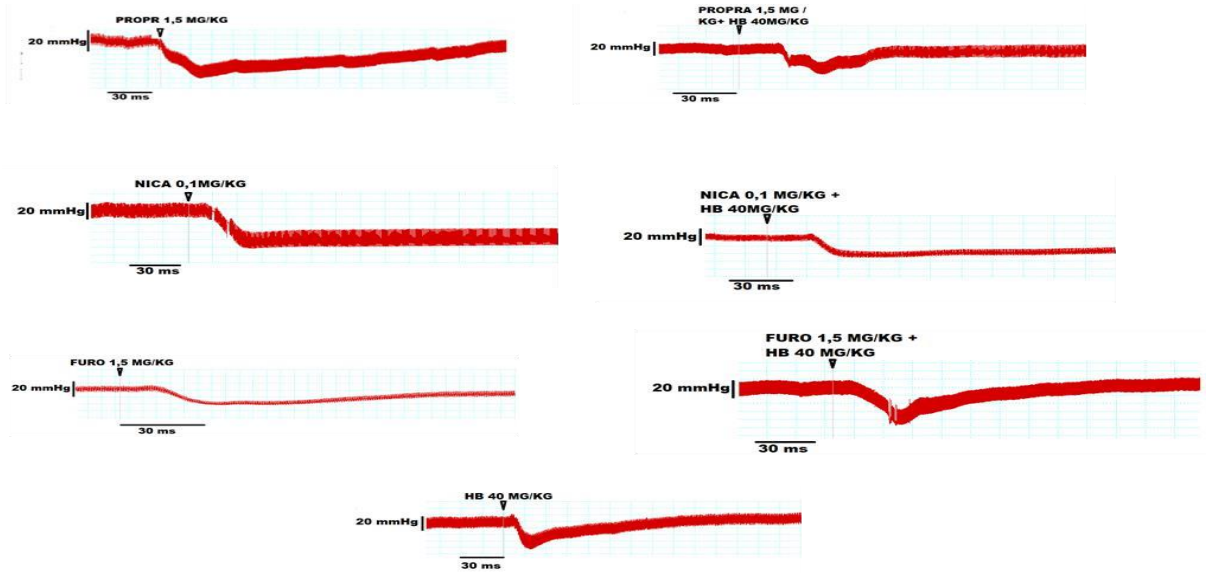

Figure 4. Impacts of *H. bonariensis* leaf extract compaired to reference drugs on rabbit blood pressure.

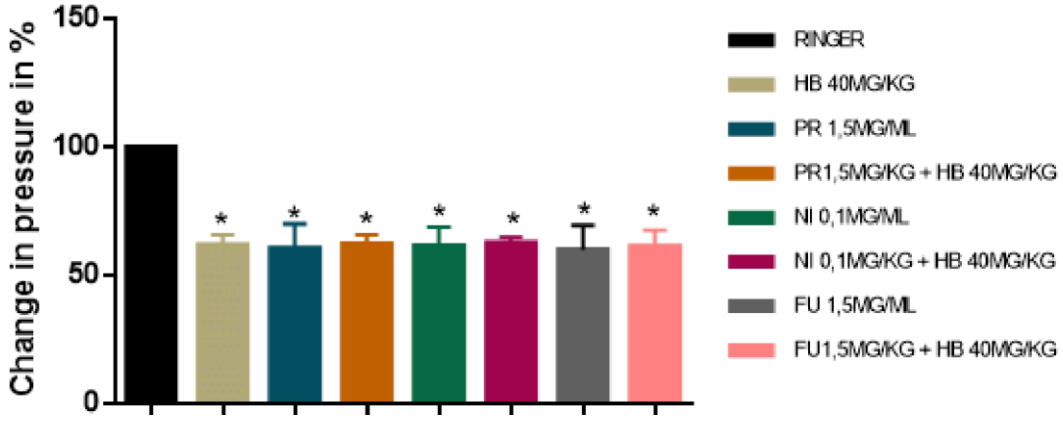

Figure 5. Impacts of the hydroethanolicleaves leaf extract of *H. bonariensis* in the presence of propranolol, nicardipine and furosemide on mean bloodl pressure (MBP) in rabbits. n = 4; *p<0.5 (ANOVA two ways + the extract + furosemide) is relatively low when the s for propranolol alone and 360.28 s for furosemide extract is involved in the treatment. This time is longer alone). As for nicardipine (both single nicardipine and when the reference molecules are injected alone (375.23 nicardipine combined with the extract), MAP decreases kruskal-wallis test). There is no significant difference between the hypotensive effects of the extract at 40 mg/kg of body weight, relative to the hypotensive effects of cardiovascular reference molecules such as propranolol at 1.5 mg/kg, furosemide at 1.5 mg/kg and nicardipine at 0.1 mg/kg. Compared to these molecules, the extract has a similar hypotensive.

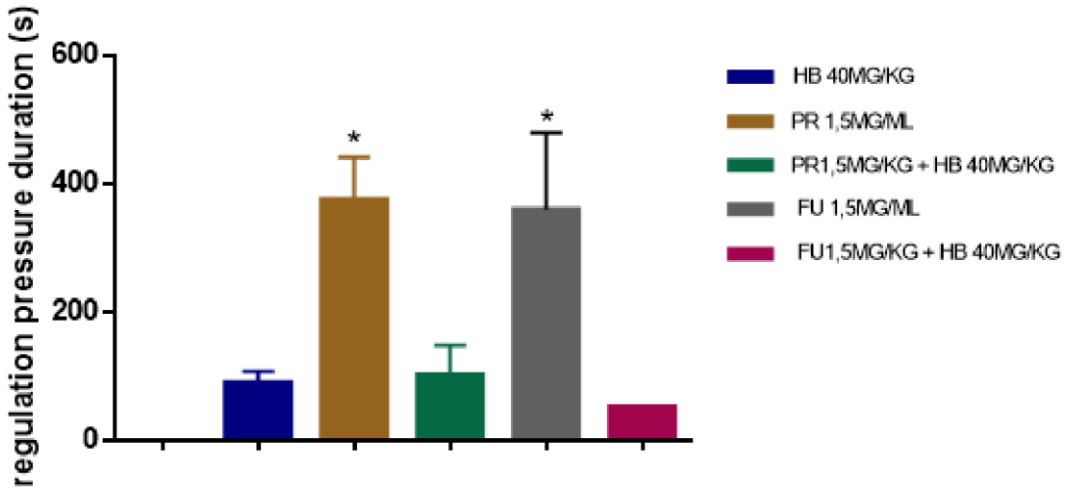

Figure 6. Impacts of hydroethanolic leaf extract of *H. bonariensis* on Mean Blood Pressure (MBP) Regulation Times (MBP) in rabbits in presence of propranolol, nicardipine and furosemide. n = 4 *p<0.5 (ANOVA one way + kruskal-wallis test). The duration of regulation of the mean arterial pressure in the presence of the extract is relatively low, compared to the reference molecules. the injection of propranolol alone or furosemide alone implies a significantly high time of return to baseline pressure compared to the injection of the extract alone as well as the injection of the extract in the presence of these same molecules. As for nicardipine, whether it is in the presence or in the absence of the extract, the return to baseline pressure is not observed.

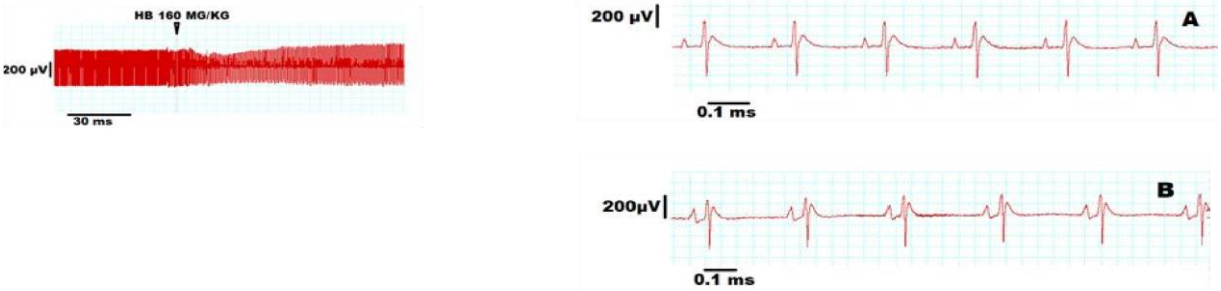

Figure 7. Effects of *Hydrocotyle bonariensis* leaves extracts on rabbit's ECG. A: control; B: HB 160 mg/kg.

DISCUSSION

The results of the present study showed that the hydroethanolic leaf extract of *H. bonariensis* greatly reduced the MBP, SBP and DBP in the rabbits. This decrease is more at the DBP level. The DBP being related to the arterial vasomotor tone, its decrease would correspond to the decrease in arterial tone induced by the extract. Therefore, this study shows that the leaves of H. bonariensis possessed a hypotensive effect. The literature indicates that more than 200 vasodilatory secondary metabolites have been identified in plants over the last three decades, while noting their structural diversity and the multiplicity of their mechanisms of action. Nevertheless, their chemical natures have allowed them to be classified. It is clear that most compounds with vasodilator activity are alkaloids, flavonoids or terpenoids (Luna-Vázquez et al., 2013). Although the mechanisms of action of these molecules are quite diverse, most of their dilatory effects involve both arterial smooth muscle and vascular endothelium. These bioactive metabolites induce vasodilation through multiple pathways at once, either by activating at least the nitric oxide/cGMP pathway or by blocking voltage-gated calcium channels (Mouzou et al., 2009; Bartáková and Nováková, 2021). Previous phytochemical studies of the leaves and rhyzomes of H. bonariensis revealed flavonoids, tannins, phenolic compounds, terpenoids, alkaloids, and saponins (Ajani et al., 2009; Masoumian et al., 2011; Tabopda et al., 2012). The presence in this plant of vasodilator compounds such as flavonoids, alkaloids and terpenoids would justify the effects observed, and these compounds would have acted on the arterial network by involving the vascular endothelium. The authors also determined the duration of regulation of MBP relative to the dose of the administered extract in order to verify whether the dose of the extract would impact the duration of its action in rabbits. They noted that the time after which ABP returns to baseline pressure following the injection of different doses of the hydroethanolic extract of H. bonariensis increases proportionally to the dose. The increase in the duration of the hypotensive effect of the extract means that the duration of the extract effect would be dependent on its bioavailability in the organism.

They compared the kinetics of the extract effect on MAP to reference molecules used in the conventional management of hypertension. Their findings revealed that there is insignificant difference between the hypotensive effects of the extract compared to the effects of the three reference molecules used (propranolol, nicardipine and furosemide). The simultaneous administration of the extract associated with each reference molecule also did not cause a significant difference in the hypotensive effect, either compared to the effect of the extract alone, or compared to the effect of each reference molecule alone. They deduce that there would be neither synergy nor antagonism between the hypotensive effects of the extract and the reference molecules. The efficacy of the hypotensive effect of the extract would therefore be similar to the hypotensive effects of these reference molecules.

Our results showed that the duration of regulation of MBP of the reference molecules alone is significantly higher compared to the extract alone and compared to the extract associated with both propranolol and furosemide. As for nicardipine, whether administered alone or in combination with the extract, it decreases MBP in rabbits irreversibly. These results showed that the duration of the extract effect is low compared to that of the reference molecules. This would imply that the period during which the extract is bioavailable would be relatively short compared to the reference molecules. This duration would be much higher for nicardipine. These effects are similar to others that have involved reference products in the evaluation of hypotensive effects of medicinal plants (Yang et al.,

2000; Leonetti et al., 2002; Yomalan et al., 2008; Traore et al., 2008; Coulibaly et al., 2017; Okemy et al., 2020).

In the present work, the impacts of the hydro-ethanolic leaves extract of H. bonariensis on the overall electrical activity of the rat heart were also evaluated. The results revealed that this extract briefly caused a significant reduction in heart rate, P-wave amplitude and QRS complex, followed by increased T-wave amplitude and RR interval duration. The QRS complex corresponds to ventricular depolarization; thus, the reduction in its amplitude would suppose that this extract can prevent ventricular depolarization and decrease the contraction force of the heart. The P wave helps to depolarize the atria and its reduction means that this extract can activate muscarinic receptors. It is reported that the activating the muscarinic receptors leads to decreased ECG or a reverse of the P wave, an expansion of the PR space and an atrioventricular disconnection (Houghton and Gray, 2005). It has been observed that the aqueous extract of Averrhoa carambola has the same impacts on the hearts of guinea pig (Vasconcelos et al., 2006) and that the hydro-ethanolic extract would contain cholinomimetic substances. The extension of the RR duration can slow down the heart contractions triggered by this extract, according to Adnet et al. (2003). This finding is verified by the decreased heart rate noticed after giving the normotensive rats the hydro-ethanolic extract intravenously. In general, these findings show a reduction in the electrical property and cardiac conduction, probably due to the cholinomimetic substances. They could also be caused by the anticalcics in the extract. In fact, the anticalcics inhibit the voltage-dependent calcium channels of type L at the level of the vessels and the heart. This makes the intracellular calcium needed for contraction not to be released (Traore et al., 2008;

Zahoui et al., 2010; Ossibi et al., 2014; Bleu et al., 2020).

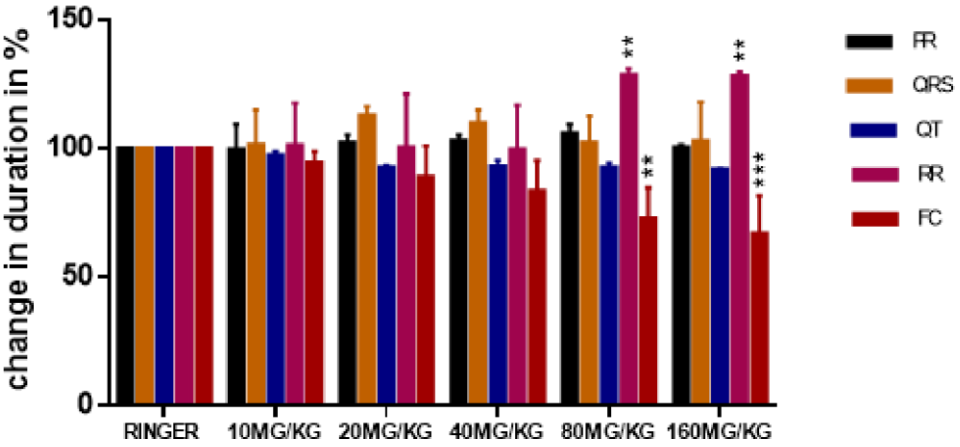

Figure 8. Impacts of hydroethanolic leaf extract of *H. bonariensis* on electrocardiogram (ECG) waves duration in rabbits. n = 4. **p < 0.01 et ***p < 0,001 (ANOVA two ways + dunnetts'test). The extract at 80 mg/kg and 160 mg/kg significantly increased the duration of the RR interval of the ECG, inducing a significant decreased heart rate. The durations of the QT, PR, P-wave, QRS and T-wave intervals were insignificantly impacted by the extract administered in the rabbits.

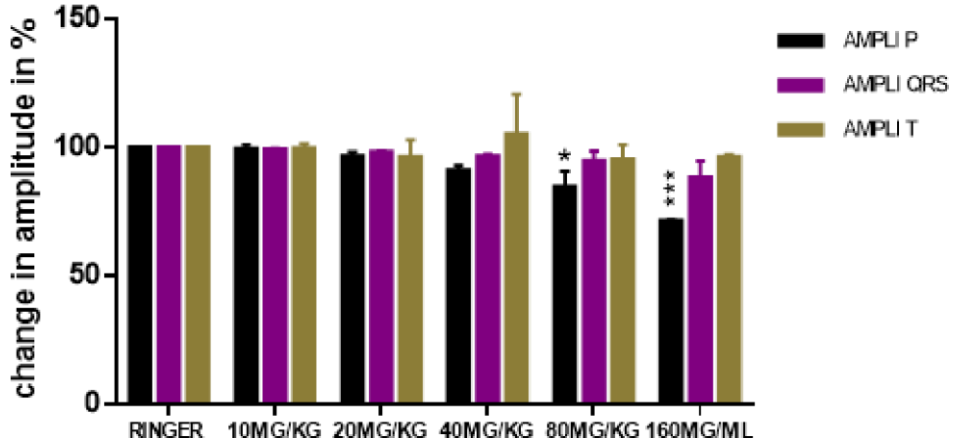

Figure 9. Impacts of hydroethanolic leaves extract of *H. bonariensis* on electrocardiogram (ECG) waves amplitude in rabbits. n = 4. *p<0.5and ***p < 0.001 (ANOVA two ways + dunnetts'test). Intravenous injection of the extract led to a great reduction in the amplitude of the P wave at the doses of 80 mg/kg and 160 mg/kg. On the other hand, the amplitudes of the QRS and T waves did not vary significantly in the presence of the extract.

Conclusion

The hydro-ethanolic leaves extract of *Hydrocotyle bonariensis* has hypotensive, inotropic and chronotropic negative effects. These effects are comparable to the effects of conventional hypotensive, which could justify its use in local drugs for the treatment of high blood pressure.

It is therefore necessary to investigate the mechanism of action, the bioactive phytochemical molecules and the bioavailability of the extract. We also plan to evaluate the same parameters at much higher doses in the future.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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