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Effects of an aqueous extract of *Bridelia ferruginea* Benth (Euphorbiaceae) on mammalian heart activity

Nene-Bi Semi Anthelme*, Zahoui Ouga Stanislas, Soro Tianga Yaya, Traore Flavien

Laboratory of Animal Physiology, UFR Biosciences, University of Cocody-Abidjan, 22 BP 582 Abidjan 22, Ivory Coast

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Abstract

Bridelia ferruginea Benth (Euphorbiaceae) is used in African traditional medicine to treat many diseases. This plant has been used as diuretic. Since, the heart activity of this substance has not been investigated in scientifically controlled studies. The aim of the present study was to evaluate the effects of an aqueous extract of *Bridelia ferruginea* (SEA) on mammalian heart activity. The extracts were administrated intravenously at doses ranging from 0.58×10^{-3} g/kg to 38.82×10^{-3} g/kg b.w. to rabbits that had been anesthetized before. SEA significantly increased the PR interval, the P and T wave amplitude and the QRS complex while the ST interval decreased. In the presence of atropine (4×10^{-1} g/kg b.w.), SEA (45×10^{-3} g/kg b.w.), significantly reduced the PR interval and caused an increase in the ST interval. At the same dose, SEA induced a decrease in the amplitude of the P wave and in the length of the ST interval after the propranolol (4×10^{-2} g/kg and 3×10^{-1} g/kg b.w.) use. The aqueous extract of this plant (10^{-8} to 10^{-2} mg/ml) induced a significant positive inotropic effect and various chronotropic effects on the isolated heart of rat. These results suggested that the extract of *Bridelia ferruginea* possess cholinomimetic and adrenomimetic substances.

*Corresponding Author: Nene-Bi Semi Anthelme ✉ neneanthelme@gmail.com

Introduction

The herbal medicine plays a very important role in health care in Africa. It is used in the treatment of several pathologies. According to Hostettmann and Potterat (1995), the active compounds from plants represent 25% of prescription drugs. This represents a total of 120 natural compounds from 90 different plants. But the use of medicinal plants is not without danger to health and poses problems of toxicity, overdose and side effects (Maiga *and al.*, 2005; Hilaly *and al.*, 2004; Sonhi, 2002; Binlin-Dadie *and al.*, 1997). From the perspective of drug development to enhance the traditional Pharmacopoeia, we undertook the pharmacological study of *Bridelia ferruginea*. *Bridelia ferruginea* (Euphorbiaceae) is a common savannah of genus *Bridelia*. Its habitat is the savannah, especially in the moister region extending from Guinea to Zaire and Angola. It is usually a gnarled shrub, which sometimes reach the size of a tree when grown in a suitable environment. The bark is dark grey, rough and even markedly scaly (Jose and Kayode, 2009; Rashid *and al.*, 2000). *Bridelia ferruginea* has diverse uses. This plant is widely used in traditional medicine as diuretic agents and purgative (Cimanga and al., 1999; Bouquet and Debray 1974). The pharmacological activities of the extracts from *Bridelia ferruginea* include anti-inflammatory (Olajide *and al.,* 2003), antibacterial and antifungal (Jose and Kayode, 2009; Talla *and al.*, 2002; Irobi *and al.*, 1994; Muanza *and al.*, 1994). This plant bark extract has been used for the coagulations of milk and also lime juice for the formulation of a traditional gargle "Ogun efu" (Orafidiya *and al.*, 1990). The aqueous extract of the stem-bark of *Bridelia ferruginea* is also used in herbal medicine as sedatives (Nene-bi *and al.,* 2010) and contains quinones, gallic and catechic tannins, alkaloids, sterols, polyterpenes, polyphenols, reducing compounds, flavonoids and saponosides (Nene-bi *and al.,* 2009). According to Nene-bi *and al.* (2008), the aqueous extract of *Bridelia ferruginea* provoked the hypotensive effect in the rabbit. In view of this, the aim of this study is to evaluate *in vivo* the effects of the aqueous extract of *Bridelia ferruginea* stem bark on global electrical activity (ECG) of the heart in the rabbit and *in vitro* the effects of the same extract on the isolated heart of rat.

Materials and methods

Plant material

The plant material of the present study, *Bridelia ferruginea* stem-bark was obtained at market from Yopougon (Ivory Coast). These stem barks were identified by an expert, Professor Ake-Assi Laurent a botanist of the National Floristic Center of University of Cocody-Abidjan (Ivory Coast). A voucher specimen (herbarium No. 17148 of August 19, 1985) was retained in this center.

Preparation of the extract

The stem barks were dried in the shade at room temperature between 26 ° C and 30 ° C and powdered with a micro-crusher. The powder obtained (50 g) was macerated for 24 hours in a 1 liter of distilled water using magnetic stirrer. The supernatant was filtered with Whatman No 1 filter paper and it was evaporated using rotating evaporator. The solvent was completely removed under reduced pressure to obtain a dry mass. The aqueous extract of *Bridelia ferruginea* stem-bark (SEA) obtained was stored at -5 ° C. The concentrations to be tested were prepared extemporaneously by dilution in Mac Ewen (ME) physiological solution of the following composition (mM): NaCl 130, KCl 2.5, $CaCl_2$ 2.42, Na_2HPO_4 1.18, $NaHCO_3$ 11.90, $MgCl_2$ 0.24, glucose 2.2 and pH=7.4.

Animals

Rabbits of *Oryctolagus cuniculus* species and rats of *Rattus norvegicus* species were used in our experiments. They were bred in animal house of UFR Biosciences (Animal Physiology laboratory, University of Cocody-Abidjan) and had access to food and water *ad libitum*. The animals were acclimatized to laboratory condition before start of experiment. All procedures were approved by the ethical committee of

Cocody University, Abidjan and conducted in accordance with the national government accepted principles for laboratory animal use and care. Rabbits and rats were anesthetized with ethyl urethane.

Recording of rabbit electrocardiograms

Rabbits weighting 1.5-2 kg were anesthetized by intraperitoneal injection of ethyl urethane (40 %)_at the dose of 1g/kg body weight (b.w.). Then each specimen was placed in the supine position. The saphenous vein from the leg was cleared. This vein is intubated with a catheter attached to a syringe allowing the injection of different doses of the aqueous extract of *Bridelia ferruginea*. The electrocardiograms (ECGs) were obtained with Cardiette Autoruler 12/1. The ECG of rabbit was recorded after drug injection as described by Traore *and al.* (2004b). Electrocardiogram (ECG) electrodes were attached to the right and left forelimb and right hindlimb for recording of ECG. ECG tracings at constant speed (25 mm/s) were analyzed and the mean values of the variables were calculated.

Recording of the contractile activity of the rat isolated cardiac muscle

Male rats weighting 150-200 g, anesthetized by intraperitoneal injection with ethyl urethane (20 %) at a dose of 1g/kg b.w. were put under artificial respiration. A thoracotomy was practised in order to reach the heart. After isolating the heart, the heparinized physiological solution was injected to dissolve possible blood clots. The isolated heart was fixed on the exit of a tap through multiple connections to bottles which contained the solutions to be tested and were oxygenated. The liquids contained in these bottles were allowed to pass by through a polyvinyl catheter, followed by the collection of serpentines in a thermostat Marie bath at 37 ° C. The apex of the heart was connected to an inscriptor stylet, which transmitted the movements on paper and moving by an engine.

Chemical used

Atropine (**ATR**) and propranolol (**PRO**) were purchased respectively from Prolabo (French) and from AstraZeneca (French).

Statistics

Statistical analysis was performed using one-way analysis of variance (ANOVA) of multiple test of comparison of Tukey-Kramer. $P<0.05$ was considered significant. All values are expressed as mean ± SEM. The GraphPad Sofware (version 4.0; San Diego, CA, USA) was used for data analysis.

Results

Effect of the aqueous extract of Bridelia ferruginea on the rabbit electrocardiogram

The intravenous administration of the aqueous extract of *Bridelia ferruginea* (SEA) provoked in anaesthetized rabbit some modifications of ECG parameters. The effect of SEA at doses ranging from 0.58×10^{-3} g/kg b.w. to 9.41×10^{-3} g/kg b.w. (Table 1) is followed by an increase in P wave amplitude (38.89 ± 8 %, $p<0.001$) and in QRS complex (50 ± 10 %, $p<0.001$). For doses ranging from 0.58×10^{-3} g/kg b.w. to 38.82×10^{-3} g/kg b.w., this extract induced a significant reduction in the ST interval (50 ± 4 %, $p<0.001$), as also an increase in T wave amplitude (200 ± 12 %, $p<0.001$) and in the PR interval (26 ± 4 %, $p<0.001$).

The effect of SEA (45×10^{-3} g/kg b.w.) on rabbit's electrocardiogram was affected in the presence of atropine (4×10^{-1} g/kg b.w.) and propranolol (4×10^{-2} g/kg b.w. and 3×10^{-1} g/kg b.w.) (Table 2). Single dose of SEA (45×10^{-3} g/kg b.w.) induced a decrease in the P wave amplitude and in the QRS complex while the T wave amplitude, significantly increased. After the atropine administration, SEA caused an increase in the ST interval, in QRS complex respectively from 24 ± 3 % ($p<0.001$) and from 85 ± 7 % ($p<0.001$) and induced a decrease in the PR length from (26 ± 5 %, $p<0.01$).

Table 1. Dose-response effects of *Bridelia ferruginea* extract on the rabbit's ECG.

ECG parameters (%)	Control	0.58×10^{-3} g/kg	3.53×10^{-3} g/kg	9.41×10^{-3} g/kg	21.18×10^{-3} g/kg	38.82×10^{-3} g/kg
P wave	0	11.11 ± 5	27.78 ± 9*	38.89 ± 8**	11.10 ± 4	5.56 ± 3
QRS complex	0	25 ± 7	40 ± 9**	50 ± 10***	25 ± 4	15 ± 4
T wave	0	50 ± 4	80 ± 9**	100 ± 11***	150 ± 9***	200 ± 12***
PR interval	0	0	16 ± 3*	16 ± 4*	24 ± 5***	26 ± 4***
ST interval	0	-25 ± 5**	-25 ±5**	-37.5 ± 4***	-50 ± 5***	-50 ± 4***

*Bidelia ferruginea extract induced the modification of the ECG parameters in rabbit (Mean ± ESM, *p<0.05; **p<0.01; ***p<0.001, n=4).*

Table 2. Effects of SEA on rabbit's heart global electrical activity in presence of atropine and propranolol.

ECG parameters (%)	Control	SEA (45.10^{-3} g/kg)	ATR (4.10^{-1} g/kg)	PRO (4.10^{-2} g/kg)	PRO (3.10^{-1} g/kg)
P wave	0	-34,33 ± 4 ***	12,33 ± 3	-13,33 ± 4	-35,33 ± 5 ***
QRS complex	0	-21 ± 5 *	85 ± 7 ***	-14 ± 4	-33 ± 5 **
T wave	0	22 ± 4 **	9 ± 3	27 ± 5 ***	53 ± 4 ***
PR interval	0	0	-26 ± 5 **	27 ± 4 **	52 ± 6 ***
ST interval	0	0	24 ± 3 ***	-26 ± 4 ***	-51 ± 5 ***

These values reflect the changes in the parameters of the ECG based on the antagonist used. The values recorded in this table are percentage changes. ***ATR****, atropine;* ***PRO****, propranolol (Mean ± ESM, *p<0.05; **p<0.01; ***p<0.001, n=4).*

In the presence of the propranolol (4×10^{-2} g/kg b.w.), SEA (45×10^{-3} g/kg b.w.) induced a decrease in P wave amplitude and in a length of the ST interval respectively from 35.33 ± 5 % (p<0.001) and from 51 ± 5 % (p<0.001). At this dose of propranolol, SEA significantly induced an increase in T wave amplitude and PR length. For the high dose of propranolol (3×10^{-1} g/kg b.w.), SEA (45×10^{-3} g/kg b.w.) caused an increase in T wave amplitude to 53 ± 4 % (p<0.001) and the PR length to 52 ± 5 % (p<0.001). In the presence of this dose of propranolol, SEA provoked a decrease in P wave amplitude, in QRS complex and in ST interval.

Effect of the aqueous extract of Bridelia ferruginea on the contractile activity of heart isolated from rat

The perfusion with different concentration of SEA affected the contractile activity of the isolated heart of the rat. For concentrations ranging from 10^{-8} mg/ml to10^{-2} mg/ml, SEA induced positive inotropic and various chronotropic effects. The concentration of 10^{-2} mg/ml of SEA significantly increased the contractile force of 26.08 ± 0.86 % (p<0.001). SEA employed in concentrations ranging from 10^{-8} mg/ml and 10^{-6} mg/ml showed a decrease in the heart rate from 21.91 ± 6.81 % and 8.22 ± 1.17 %. For concentrations from 10^{-4} mg/ml and 10^{-2} mg/ml, that extract induced an

increase in the heart rate from 80.07 ± 3.27 % (p<0.01) and 53.3 ± 5.69 % (p<0.001) (Fig. 1).

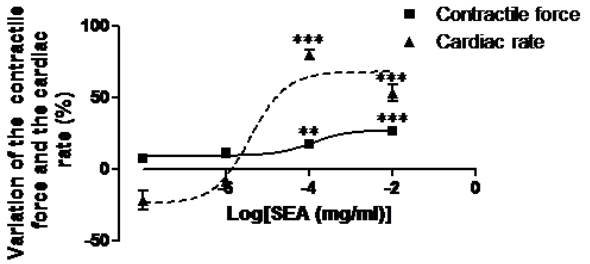

Fig. 1. Concentration-response effect of SEA on the mechanical activity of isolated heart in rat. SEA induced a positive inotropic effect, negative and positive chronotropic effect. These values express percentage changes of maximum amplitude and heart rate compared with the control, (Mean ± ESM, **p< 0.01; ***p< 0.001, n=5).

Discussion

The present study has demonstrated that in mammalians cardiac activity, SEA induced a biphasic effect. At doses, ranging from 0.58×10^{-3} g/kg b.w. to 38.82×10^{-3} g/kg b.w., our studies show that SEA provoked a variation of the rabbit electrocardiogram parameters. For doses ranging from 0.58×10^{-3} g/kg b.w. to 9.41×10^{-3} g/kg b.w., SEA induced the cardiotonic effect with an increase in P wave amplitude and in QRS complex. At the dose higher than 9.41×10^{-3} g/kg b.w., this extract induced a decrease in P wave amplitude and in QRS complex but caused an increase in T wave and in PR interval. SEA could reduce the heart rate with an increase of the PR interval. In the presence of the atropine and the propranolol, the effects induced by SEA on the ECG parameters were affected. These observations were compatible with the presence of cardiotonic and cardiodepressive substances in the aqueous extract of *Bridelia ferruginea*. These results show that SEA as well as *Heliotropium indicum* and *Zizyphus mauritiana* could contains cholinomimetic and adrenomimetic substances (Traore *and al*., 2004b). According to Traore *and al*. (2004a) through a pharmacological study on the duodenal smooth muscle of rabbit, SEA contains cholinomimetic and adrenomimetic substances.

For concentrations ranging from 10^{-8} mg/ml to 10^{-2} mg/ml on the isolated heart from rat, SEA induced positive inotropic and various chronotropic effects. SEA in concentrations ranging 10^{-8} mg/ml to10^{-6} mg/ml induced negative chronotropic effect. At the concentration higher than 10^{-6} mg/ml, SEA caused positive chronotropic effect. The negative chronotropic effect of SEA is believed to participate in the effects of cholinergic attenuation of heart rate. The Acetylcholine fixation can decrease Ca^{2+} entry to the cell, which can in turn result in reduction of contractile force (Wang *and al*., 2004). The positive inotropic and chronotropic effects of SEA were compatible with the presence of adrenomimetic substances which could increase L-type Ca^{2+} channel conductance (Bers, 2002; Bers, 1991) and contractile force (Galli *and al*., 2006; Overgaard *and al*., 2005; Nielsen and Gesser, 2001; Ball and Hicks, 1996).

In conclusion these observations suggest that the aqueous extract of *Bridelia ferruginea* contains cholinomimetic and adrenomimetic substances which induce respectively cardiopdepression and cardioacceleration effects. These results support further the use of the aqueous extract of *Bridelia ferruginea* in the traditional African medicine in the treatment of various diseases.

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