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# PHARMACOLOGICAL EFFECTS OF AN AQUEOUS EXTRACT OF *PICRALIMA NITIDA* (STAPF) (APOCYNACEAE) ON THE CARDIOVASCULAR SYSTEM AND THE INTESTINE OF MAMMALS

## ABSTRACT

Picralima nitida, aplant of African pharmacopoeia is used in the treatment of diseases such as malaria, typhoid fever and anemia. To promote this herb, we undertook to study its effect on the cardiovascular system and the smooth duodenal muscle.The study of this extract on the electrocardiogram of rabbits at doses of between $2.7\times10^{-3}$ g/kg and $3.4\times10^{-2}$ g/kg bw, showed that Pn causes an increase of the durations of PR and ST spaces respectively of 0.11 ±0.01 ($p<0.001$) and 0.14±0 sec ($p<0.001$) and a decrease in heart rate significantly ($p <0.001$).In the presence of propranolol ($5.6\times10^{-7}$-$5.6\times10^{-4}$ g/kg), Pn ($3.9\times10^{-2}$ g/kg) causes a decrease of the P-wave and the heart rate, an increase in the amplitude of the T-wave and the duration of the ST space. The amplitude of the QRS complex decreases before rising to high doses of propranolol.On the isolated heartof rat, the extract induced the positive chronotropic and inotropic effects for concentrations between $10^{-10}$ mg/ml and $10^{-6}$ mg/ml. Indeed, the extract causes an increase of the cardiacrate and amplitude respectively of 108.67±4.67% ($p<0.05$) and 219.6±5.43% ($p<0.001$).On the smooth muscle of duodenum of rabbit, Pn decreases the amplitude of the contractions depending of the concentration with a maximum effect ($p<0.001$) at $4\times10^{-4}$ g/ml.In the presence of propranolol ($4.10^{-10}$g/ml), the negative inotropic effects of Pn at $4\times10^{-4}$g/ml were reduced by 52%.The results of this study show that this extract contains adrenomimetics substances inhibited by propranolol.

**Keywords** Picralima nitida, Propranolol, adrenimimetiques Substances, cardiac and intestinal activity.

## INTRODUCTION

African traditional medicine often uses the plants in the treatment of diseases. To enhance this herbal medicine, we conducted a pharmacological study of Picralima nitida also called *Picralima macrocarpa* or *Picralima kleineana* or *Tabernaemontana nitida*[1]. It is a deciduous tree of about 20 meters high widespread in intertropical forested areas of Africa from Côte d'Ivoire (Ivory Coast) to Uganda through Zaire[2-6]. The fruits are large ovoid, yellowish when ripe. Seeds are obliquely oval, obovate to oblong, flattened from2.5 to 4.5 cm long, smooth, wrapped in a soft pulp [5-6].This plant is used in traditional medicine in the treatment of diseases such as malaria, typhoid fever, anemia, jaundice and dysmenorrhea [7]. The previous pharmacological studies have shown that the extracts of this plant would possess the sympathicostenics activities, antimalarial, antipsychotic and local anesthetic equivalent to that of cocaine [8-11].It would also have antimicrobial properties [12-13], hypoglycemic [14-16] and anti-diarrheal [17].In order to assess the effects of Picralima nitida, we decided to study the effects of crude extract of the seeds of this plant on the cardiovascular system and the activity of smooth intestine muscle of mammals.

## MATERIALS AND METHODS

### Plant material

The seeds of *Picralima nitida* were purchased from an herbalist in yopougon market in the north of Abidjan (Côte

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d'Ivoire). They were identified by an expert in botanic systematic, professor Ake-Assi of the national floristic centre of University Felix Houphouet-Boigny.

**Preparation of the aqueous extract of *Picralima nitida* seeds**

The *Picralima nitida* seeds from dry fruits were ground with micro-crusher (Culatti, France). The powdered (5 g) of seed was diluted in 50 ml of boiled distilled water at 100° C during 15 minutes. The infused is cooled and the solution obtained was filtered through of wattman paper n°1. The filtrate was frozen at -30° C and lyophilized at -45° C using a lyophilisator (Telstar, Spain). A brown colored powder was obtained. It is stored in the refrigerator at -5° C in a sealed jar.

**Animal material**

The animals used in our experiments consist of rat (Rattus norvegicus) and rabbit (Oryctolagus cuniculus). The tests were performed only after that, rats were acclimated to the environment of the animal house of Biosciences. All procedures were approved by ethical committee of University Felix Houphouet-Boigny (Côte d'Ivoire) and in accordance with the principles of scientific ethical committee of biology for use of laboratory animals for experimental tests[18].

**Recording of rabbit electrocardiograms**

Rabbits weighting approximately 1.45 kg, were anesthetized by intraperitoneal injection of ethyl urethane (40 %) at the dose of 1g/kg body weight (bw). Then each specimen was placed in the supine position. The saphenous vein from the leg was bared. This vein is intubated with a catheter attached to a syringe allowing the injection of different doses of the aqueous extract of Picralima nitida. The electrocardiograms (ECGs) were obtained with Cardiette Autoruler 12/1. The electrodes of Electrocardiograph were attached to the forelimbs and hindlimbs as described by Traore etal. [19]. The 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**

The male rats weighing between 100 and 200g were used. They were anesthetized with ethyl urethane injection (20%) by intraperitoneal route at the dose of 1g / kg body weight and placed under artificial respiration. A thoracotomy is performed to quickly isolate the heart. A solution of Mac Ewen((mM): NaCl 130; KCl 2.5; CaCl2 2.4; NaH2PO4 1.18; NaHCO3 11.9; MgCl2 0.24; glucose 2.2)heparin is injected through the aorta to prevent blood clotting in the heart. The heart is then connected to the output of a multi-way valve topped of buckets containing oxygenated physiological solutions and the solutions to perfuse the isolated heart of rat. The solutions contained in these buckets, pass through polyvinyl catheters immersed in a water bath thermostated at 37 °C. The apex of the heart is connected to a stylus which will transmit the movement of the heart on the cylinder covered with a smoky paper driven by motor.

**Recording Method rhythmic contractions of the isolated intestine of rabbit**

After fasting for 24 hours, the rabbit was sacrificed by cervical dislocation. A laparotomy was performed, and then a piece of duodenum about 3 cm was removed and preserved in physiological solution of Mac Ewen type. This

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solution is oxygenated, and its temperature is maintained at 38 °C. Using wire passed through the wall of the intestine fragment, a node is formed at one end of the duodenum fragment to be able to hang the support of organ bath. The other end is connected by a wire to therecorder, whose pen rubs on a cylinder covered by smoky paper driven by a motor.

**Statistical Analysis**

The statistical analysis was performed using one-way analysis of variance (ANOVA) of the multiple test of comparison of Tukey-Kramer (GraphPad Prism software, version 4, San Diego, USA). The level of significance was determined in comparison with the control group. $p<0.05$ was considered significant. All values are expressed as mean ± SEM.

**RESULTS**

**The effects of the aqueous extract of Picralima nitida (pn) on rabbit electrocardiogram**

**Effect of the extract of Pn on electrocardiogram of rabbit**

The figure 1 shows the dose-response effect of Pn on the overall electrical activity (ECG) of rabbit heart.

For doses between $2.7\times10^{-3}$ g/kg bw and $3.4\times10^{-2}$ g/kg bw, Pn causes a non-significant increase in the amplitude of the P wave, QRS and T with respective values of 0.23 ± 0.3 mV ($p> 0.05$), 0.47 ± 0.02 mV ($p> 0.05$) and 0.2 ± 0.02 mV ($p> 0.05$). The duration of the PR and ST spaces increased respectively of 0.11 ± 0,01sec ($p <0.001$) and 0.14 ± 0 sec ($p <0.001$). The heart rate, in turn, is significantly reduces ($p <0.001$) in the same dose range.

The figure 2 reflects the mean changes of the amplitude of the P wave, QRS, and T, the durations of the PR and ST spaces and the heart rate depending of the dose of Pn. The experiments were carried out several times (n = 3).

**Effect of Pn on electrocardiogram of rabbit in the presence of propranolol (PRO)**

The figure 3 shows the dose-response effect ofPnon the overall electrical activity (ECG) of rabbit heart in the presence of propranolol.

Pn($3.9\times10^{-2}$ g/kg bw), induces an increase in the amplitude of the P waves, QRS and T. The duration of ST and PR spaces increased. The heart rate decreases significantly.

In the presence of propranolol ($5.6\times10^{-7}$g/kg to $5.6\times10^{-4}$ g/kg of bw), Pn causes a reduction of the Pwave. The amplitude of the QRS complex decreases before to rise to high doses of propranolol. The amplitude of Twave, increases.

The duration of ST space increases while thatof PRremain constant.

In the presence of propranolol, heart rate decreased from 243 ± 1 beats/min ($p <0.001$) to 183.67 ± 1.53 beats/min ($p <0.001$).

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The mean values obtained after several experiments (n = 3) are the variations, shown in table I.

**Study of the effects of aqueous extract of Picralima nitida (Pn) on the contractile activity of isolated heartof rat**

The dose-response effect of Pn on the contractile activity of isolated heart of rat is shown in figure 4.

Figure 4A is a original recording of this effect at concentrations between $10^{-10}$ mg/ml and $10^{-2}$ mg/ml.Pn has a positive inotropic effect, of which the maximum effect corresponding an increase of amplitude of 219.6 ± 5.43% ($p < 0.001$), was obtained at $10^{-6}$ mg/ml.

In the same concentration range, Pn induces a dose-dependent positive chronotropic effect (Figure 15A), with the maximum effect equal to 108.67 ± 4.67% ($p < 0.05$), is recorded at $10^{-2}$ mg/ml.The experiments were carried out several times (n = 3) and the mean values obtained were allowed to draw the curves in figure 4Breflecting the variations of the amplitude of contractions and the heartrate induced by Pn.

**Study of the effects of aqueous extract of *Picralima nitida* (Pn) on isolated duodenum of rabbit**
**Dose-response effect of *Picralima nitida* (Pn) on the rhythmic contractions of duodenum of rabbit**

The figure 5A shows the decrease in the contractile activity of the isolated duodenum of rabbit, depending on the concentration of Pn.Between $2\times10^{-4}$ g/ml and $4\times10^{-4}$ g/ml, Pn causes a decreases in the amplitude of rhythmical contractions, between 121 ± 1.64% ($p > 0.05$) and 277.67 ± 14.68% ($p < 0.001$).

The experiments were carried out several times (n = 4) and the values average obtained are allowed to trace the curve of figure 5B reflecting the decrease in the amplitude of the rhythmic contractions of the isolated duodenum of rabbit depending on the concentration of Pn.

**Dose-response effect of Picralima nitida (Pn) on the rhythmic contractions of rabbit's duodenum in the presence of propranolol (PRO)**

Figure 6A shows the effects of Pn on the isolated duodenum of rabbit in the presence of propranolol. Between $2\times10^{-4}$ g/ml and $4\times10^{-4}$ g/ml, in the presence of propranolol $4\times10^{-10}$ g/ml, Pn induces a decreases in the amplitude of the rhythmic contractions of the duodenum between 73 ± 5% ($p > 0.05$) and 133.33 ± 5% ($p < 0.001$).

The experiments were carried out several times (n = 4) and the obtained average values are allowed to trace the curve of figure 6B reflecting the changes in the amplitude of rhythmic contractions of rabbit duodenum depending on the concentration of Pn.

**DISCUSSION**

The study of the pharmacological effects of the aqueous extract of the seeds of Picralima nitida shows that this

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extract at concentrations between $10^{-10}$ mg/ml and $10^{-2}$ mg/ml, has the positive chronotropic and inotropic effects on the isolated heart of rat. These effects are similar to those observed with extracts of Rosa Damascena[20]and Leonotis leonurus [21], respectively, over the heart of rat and guinea pig.

Between $2.7\times10^{-3}$ g/kg bw and $3.4\times10^{-2}$ g/kg bw, Pn causes a small increase in P waves, QRS and T of ECG of rabbit and a sharp increase of PR and ST spaces, as well as a significant decrease in heart rate.

The same aqueous extract causes a reduction in the amplitude of rhythmical contractions of the smooth muscle of the rabbit duodenum. This negative inotropic effect is identical to that induced by the aqueous extracts of the stem bark of Spondias mombin on the duodenal smooth muscle of rabbit [22].

The increase of the P waves, QRS and ST space of ECG, the decrease of contractions of the intestinal smooth muscle thus that the increases of the amplitude and rate of the heart are well-known effects of adrenaline.

Thereby propranolol, anantagonist of β-adrenergic receptors [23-25], was used as an antagonist of Pn. The antagonism study of propranolol-Pn on the ECG and the rhythmics contractions of duodenal smooth muscle of rabbit, shows a significant decrease in positive effects induced by the extract on P waves, QRS and ST space of ECG and the negative effect recorded on the contraction of duodenal smooth muscle of rabbit.

These results suggest the presence of the adrenomimetics substances of β-adrenergic type in the aqueous extract of Picralima nitida. These substances might, such as adrenaline, activate β-adrenergic receptors which predominate in the heart and intestinal tissues [26-27].

The stimulation of the β-adrenergic receptor is responsible of the positive chronotropic and inotropic effects on the heart [28,24,29]. These effects would be due to the activation of the Gs subunit of the G-protein which will activate the production of cAMP by an adenylate cyclase [30-32].

Conversely, stimulation of the β-adrenergic receptor induced negative inotropic effects on the duodenal smooth muscle. These effects are due to the activation of the Gi subunit of the G-protein, which in contrast to the Gs subunit, inhibits the adénylclase, reducing the formation of cAMP [27].

In addition to these effects similar to those induced by catecholamines such as adrenaline, the aqueous extract of Picralima nitida also induces effects similar to those of acetylcholine.

Indeed, Pn induces an increase of the T-wave and PR interval of the ECG and a decrease of the heart rate.These results corroborate those obtained during the study of Pn effects, on blood pressure of rabbit [33].In the aqueous extract of *Picralima nitida* would find the adrenergic and cholinergic substances, as in extracts of *Bridelia ferruginea*[34-35] and *Heliotropium indicum*[36].The partial blocking of the hypotension induced by Pn, on the arterial blood pressure of rabbit by atropine [33] and the partial inhibition of the negative inotropic effect of Pn, on the intestine of rabbit and the decreasing the of effects of the same extract on the P waves and QRS of rabbit's ECG by propranolol, indicate the presence in this extract other substances pharmacodynamic insensitive to propranolol and atropine.

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## CONCLUSION

In addition of cholinomimetic substances of muscarinic type identified in the study of pharmacological effects of Pn on blood pressure rabbit, the works on the cardiovascular system and the mammalian duodenum, proves in the same extract the presence of adrenomimetics substances of beta (β) type.

The different pharmacological effects observed militate in favor of using this herb for the treatment of several diseases.

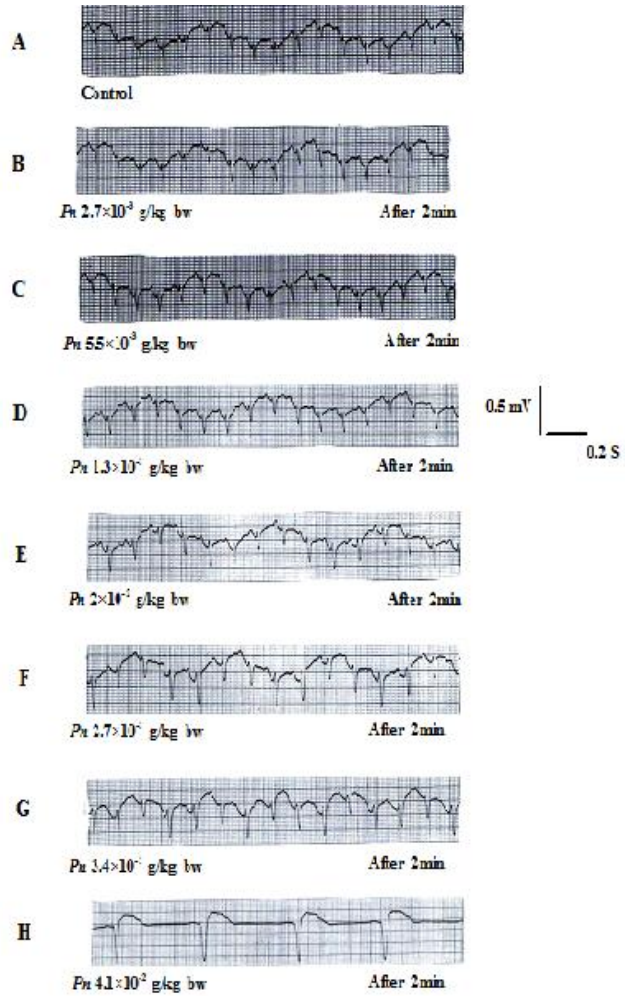


**Figure 1: Dose-response effect of Picralima nitida on the electrocardiogram (ECG) of rabbit. A:** Normal recording.**B**to**H** Effect ofPn at $2.7\times10^{-3}$ g/kg bw (**B**); $5.5\times10^{-3}$ g/kg bw(**C**); $1.3\times10^{-2}$ g/kg bw(**D**); $2.10^{-2}$ g/kg bw(**E**); $2.7\times10^{-2}$ g/kg bw(**F**); $3.4\times10^{-2}$ g/kg bw(**G**); $4.1\times10^{-2}$g/Kg bw (**H**) 2mn after injection. Pn changes significantly, the characteristics of the ECG of rabbits at doses ranging from$2.7\times10^{-3}$ to $3.4\times10^{-2}$ g/kg bw.

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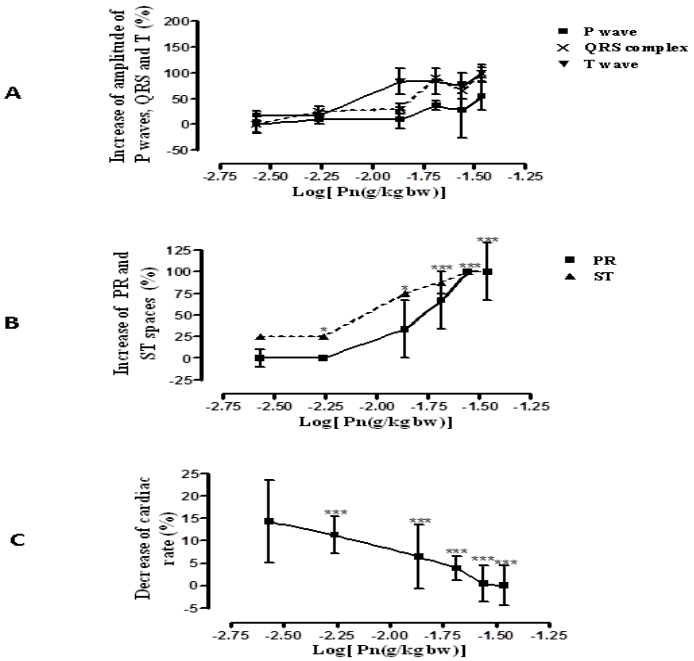


**Figure 2: Variation of the characteristics of the rabbit's electrocardiogram in function of increasing doses of Picralima nitida(Pn). A:** increasing of the amplitude of the P, QRS and T waves of the ECG.**B :** Increasing of the PR and ST spaces of ECG. **C :** Decreasing of the heart rate.Pn causes an increase in the amplitude of the P, QRS and T waves, PR and ST spaces and a decrease in the heart rate.The values express the percentage of variations (mean ± SEM, * p <0.05, *** p <0.001, n = 3)

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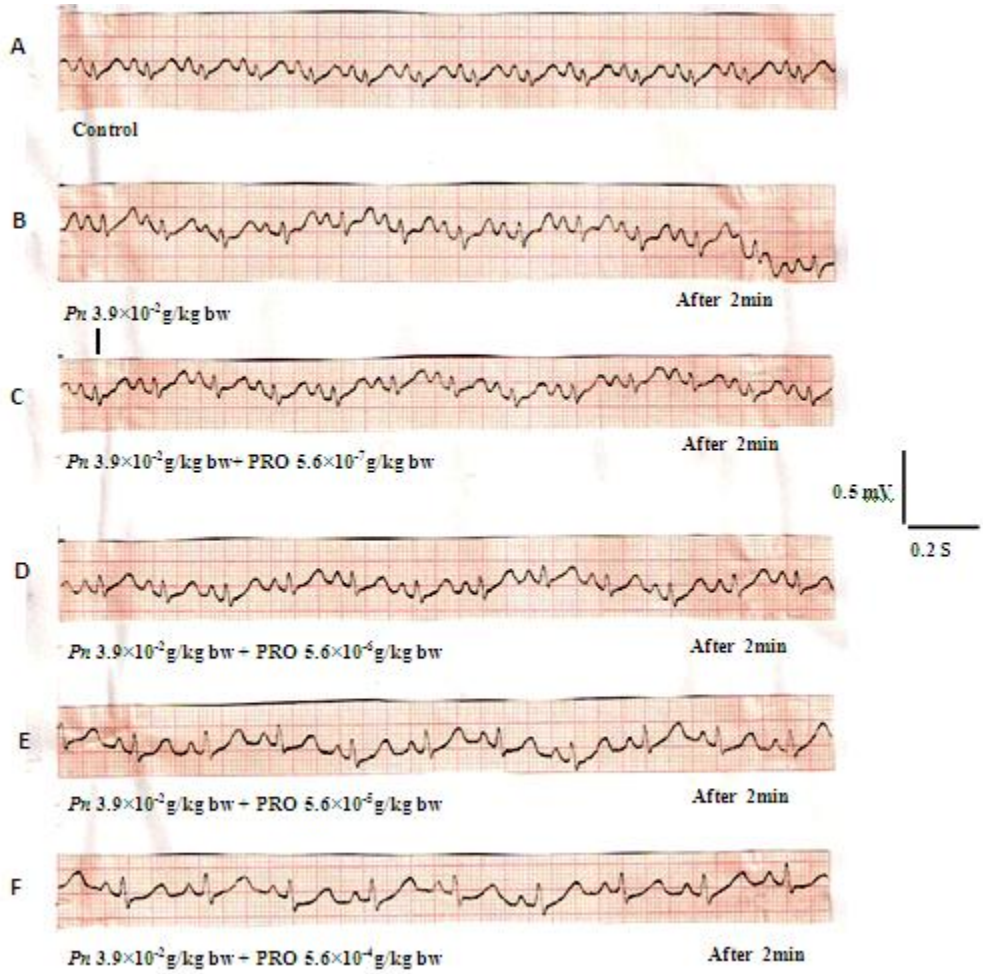


**Figure 3: Effect of Picralima nitida on rabbit's electrocardiogram in the presence of propranolol. A**: Original recording.**Bto E**: Effect of Pn at $3.9\times10^{-2}$ g/kg bw (**B**)followed by those of propranolol $5.6\times10^{-7}$ g/kg bw (**C**), $5.6\times10^{-6}$ g/kg bw (**D**), $5.6\times10^{-5}$ g/kg bw (**E**), $5.6\times10^{-4}$ g/kg bw (**F**).Pn significantly modifies the characteristics of the ECG in the presence of propranolol for the doses ranging from $5.6\times10^{-7}$ g/kg to $5.6\times10^{-4}$ g/kg bw.

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| | Control | *Pn* ($3.9\times10^{-2}$g/kg) | PRO ($5.6\times10^{-7}$g/kg) | PRO ($5.6\times10^{-6}$g/) | PRO ($5.6\times10^{-5}$g/kg) | PRO ($5.6\times10^{-4}$g/kg) |
|---|---|---|---|---|---|---|
| Amplitudes of P wave (mV) | 0.175 ± 0.025 | 0.183 ± 0.014 | 0.167 ± 0.014 | 0.150 ±0.000 | 0.133 ± 0.014 | 0.117 ± 0.014** |
| Amplitudes of QRS complex (mV) | 0.167 ± 0.014 | 0.242 ± 0.014** | 0.225 ± 0.025* | 0.217 ± 0.029 | 0.292 ± 0.014** | 0.317 ± 0.014*** |
| Amplitudes of T wave (mV) | 0.133 ± 0.029 | 0.208 ± 0.038 | 0.217 ± 0.029* | 0.225 ± 0.025* | 0.267 ± 0.029** | 0.283 ± 0.029*** |
| Durations of the ST space(sec) | 0.097 ± 0.015 | 0.113 ± 0.011 | 0.117 ± 0.006 | 0.117 ± 0.006 | 0.127 ± 0.006* | 0.143 ± 0.006*** |
| Durations of the PR space (sec) | 0.060 ± 0.000 | 0.070 ± 0.000 | 0.070 ± 0.000 | 0.070 ± 0.000 | 0.070 ± 0.000 | 0.070 ± 0.000 |
| Herat rate(beats/mn) | 274.33 ± 5.13 | 249 ± 3.61*** | 243 ± 1*** | 212 ± 3*** | 185.33 ± 2.52*** | 183.67 ± 1.53*** |

**Table 1 : Effect of the extract of Picralima nitida on the characteristics of the ECG of rabbit in the presence of propranolol**

These values express the changes in the characteristics of the ECG depending of doses of propranolol (PRO). The values in the table are percentages of variations (mean ± SEM, * p <0.05, ** p <0.01, *** p <0.001, n = 3).

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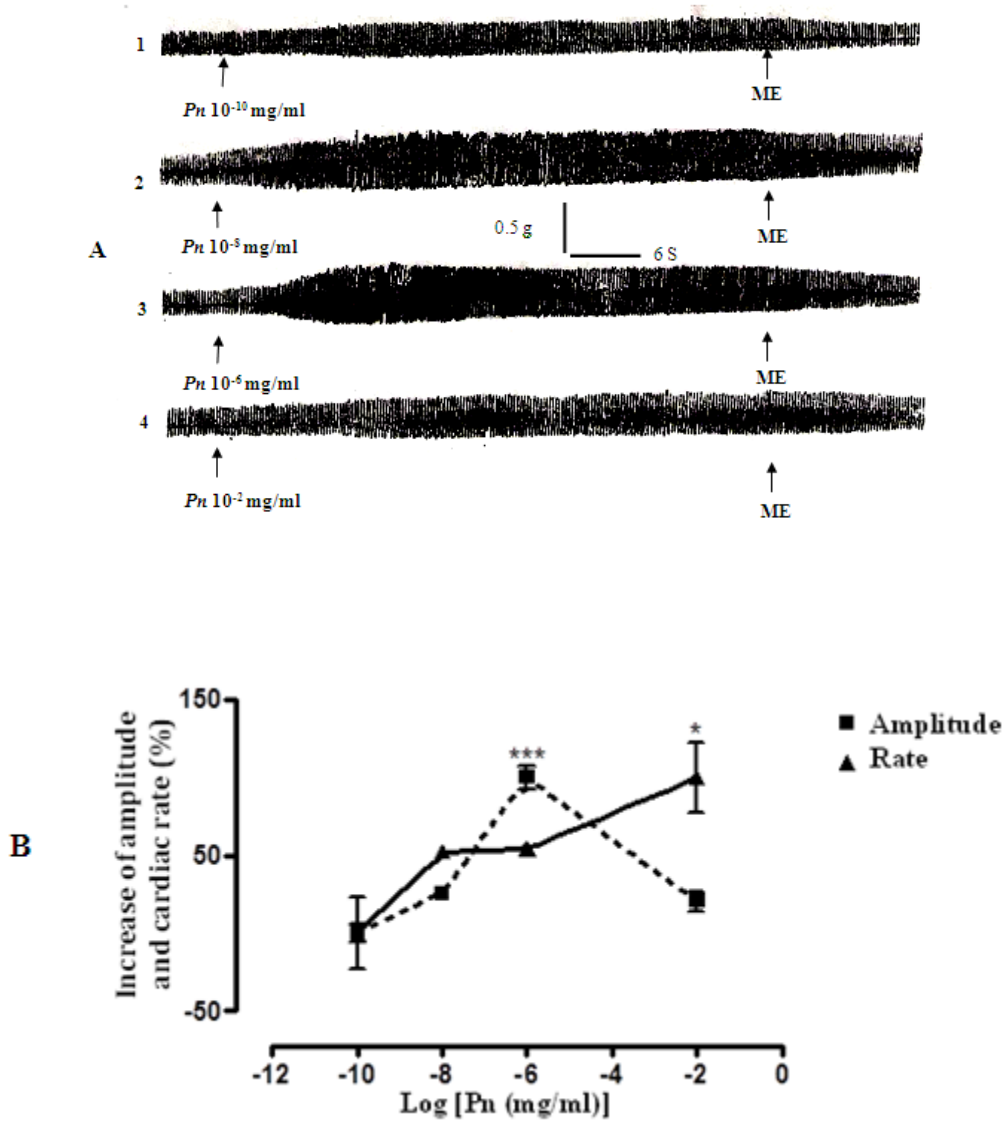


**Figure 4: Dose-response effect of the extract of *Picralima nitida* (*Pn*) on the mechanical activity of isolated heart of rat.**

**A: Effect of *Pn* on the mechanical activity of the heart in function of concentration: 1 à 4 :** Effect of*Pn*at $10^{-10}$ mg/ml (**1**); $10^{-8}$ mg/ml (**2**); $10^{-6}$ mg/ml (**3**); $10^{-2}$ mg/ml(**4**).*Pn induced positive inotropic and chronotropic effects.*

**B: Variation of the amplitude and frequency of contractions of the heart in function of the concentration of *Pn* :***These values indicate the percentages of maximum variation of the amplitude and the heart rate, compared to*

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*control recording (mean ± SEM, * p <0.05; *** p <0.001, n = 3).*

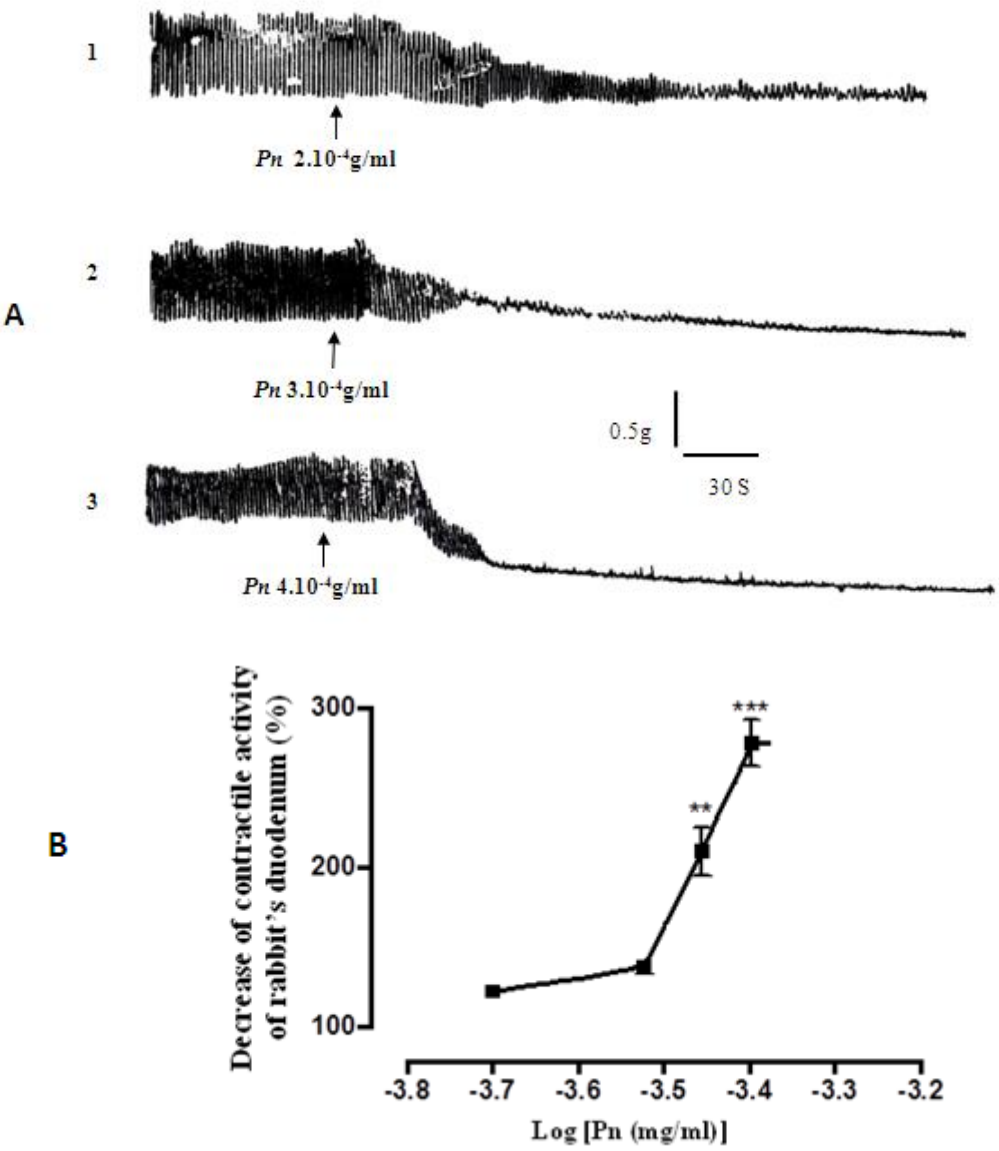


**Figure 5 : Effect of the extract of *Picralima nitida* on rhythmic contractions of the isolated duodenum of rabbit . A:** Dose-response effect of the extract of *Picralima nitida* (*Pn*). **1** to **3**: *Pn* effect $2.10^{-4}$ g/ml (**1**), $3.10^{-4}$ g/ml (**2**), $4.10^{-4}$ g/ml (**3**). *Pn* causes a dose-dependent decrease in contractions. **B**: Reduction of rhythmic contractile

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activity of isolated rabbit duodenum depending on the concentration of *Pn*. The values express the maximum decrease in percentages versus to the normal recording (mean ± SEM ** p <0.01, *** p <0.001, n = 4).

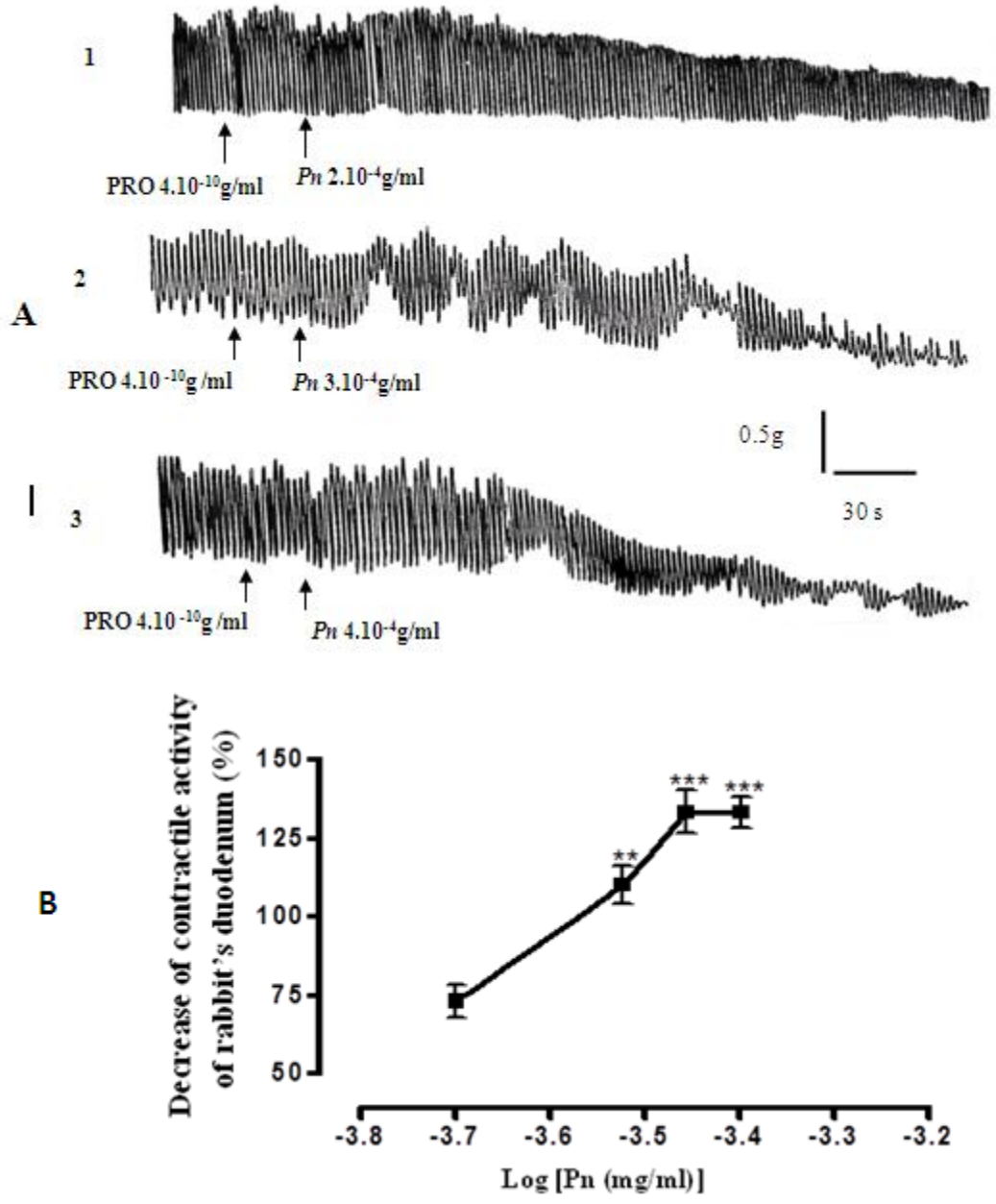


**Figure 6: Effect of *Picralima nitida* (*Pn*) on the isolated rabbit intestine in the presence of propranolol (PRO).** **A:** Pn effect in the presence of propranolol. **1** to **3**: Effect of Pn $2.10^{-4}$g/ml (**1**); $3.10^{-4}$g/ml (**2**); $4.10^{-4}$g/ml (**3**) in the

presence of propranolol ($4.10^{-10}$ g/ml). Propranolol partially inhibits the decrease in dose-dependent contractions induced by Pn. **B**: Decrease of intestinal contraction depending on the concentration of Pn in the presence of propranolol. The values express the maximum decrease in percentages versus to the normal recording (mean ± SEM ** p <0.01, *** p <0.001, n = 3).

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