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# Pharmacological effects of an aqueous leaf extract of *Lophira lanceolata* (Ochnaceae) on blood pressure and electrocardiogram in anesthetized rabbits

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## Abstract

Arterial hypertension is a cardiovascular disease prevalent in black African countries. Its prevalence is 5 to 20% in sub-Sahara African countries and 20% in Côte d'Ivoire. Despite the variety of antihypertensive drugs available in modern medicine, the disease persists. Hence the search for natural products with potential anti-hypertensive properties is ongoing. This study focused on the effects of aqueous leaf extract of *Lophira lanceolata* on the arterial blood pressure (BP) and electrocardiography (ECG) in rabbits.

Phytochemical analysis was carried out in order to determine the phytoconstituents contained in the extract. Varied *L. lanceolata* macerate doses (0.5 to 50 mg/kg bw) were administered to anesthetized rabbits intravenously. The carotid artery was intubated using a catheter connected to Ludwig's mercury manometer for BP measurement. The recording of the ECG was performed using an electrocardiograph.

The phytochemical screening revealed the presence of phytoconstituents including polyphenols, flavonoids and alkaloids in *L. lanceolata*. The results showed that *L. lanceolata* induced a dose-dependent hypotension with a fifty percent effective dose ($ED_{50}$) equal to 5.36 mg/kg bw. in normotensive rabbits. The hypotension induced by the extract was significantly ($p<0.01$) reduced up to 60% by atropine, an acetylcholine muscarinic receptor antagonist. In addition, the extract significantly ($p<0.001$) decreased the hypertension induced in rabbits with adrenaline up to 70%. On the ECG, the extract caused significant decreases ($p<0.001$) of the amplitudes of the P waves, T waves, the QRS complex and the PQ and QT intervals. However, the heart rate increased significantly ($p<0.001$). The usefulness of *L. lanceolata* in traditional medicine for the treatment of hypertension is potentiated. It is therefore important to encourage its use.

**Keywords:** *Lophira lanceolata*; Blood pressure; Electrocardiogram; Phytoconstituents; Rabbits

## 1. Introduction

Hypertension (high blood pressure) is a devastating medical condition in which the blood vessels have persistently raised pressure [1]. Each time the heart beats, it pumps blood into the vessels (arteries). Blood pressure (BP) is then created by the force exerted by the blood on the walls of blood vessels as it is pumped by the heart [2]. Classified as a non-communicable disease, arterial hypertension is the most widespread cardiovascular disease in black Africa population [3]. It is characterized by increase in systolic and/or diastolic pressures (higher than 160 mmHg and 95

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mmHg respectively), it constitutes a public health problem with very serious consequences including about 51% of cases of cerebrovascular disease worldwide (Wajngarten and Silva, 2019) [4, 5].

Approximately one-quarter of the global adult population is hypertensive and this proportion is expected to reach 29.2% (about 1.6 billion people) by 2025. Out of total 58.8 million deaths worldwide in year 2004, high blood pressure was responsible for 12.8% (7.5 million deaths) [6,7]. In sub-Saharan Africa, this condition currently affects approximately 27-28% of the adult population of age 20 and above. The World Health Organization (WHO) in 2005 estimated the overall prevalence of arterial hypertension in Côte d'Ivoire to be 21.7% and this was significantly more important in rural areas with 29.6% against 21% in urban areas [8].

The prevalence of hypertension has increased, especially in low-income countries. Despite the increasing prevalence, the proportions of hypertension awareness, treatment and BP control are low, particularly in low-income countries, and few comprehensive assessments of the economic impact of hypertension exist [9]. Various anti-hypertensive drugs have been used in the treatment of hypertension. Though most these medicines have been found helpful, they nevertheless come with several problems such as side effects and high cost, which limit their extensive use [10, 11, 12]. Hence studies are warranted on implementation of novel strategies for hypertension prevention, treatment and control.

Indeed, it is well known that plants, the main therapeutic means in Africa, are used by more than 80% of the population [13]. 50,000 species of vascularized plants used in the treatment of various conditions have been identified in Africa [14]. In Côte d'Ivoire, 1421 species of medicinal plants and 761 medicinal recipes have been listed [15]. *L. lanceolata* is included in this list. Its leaves are used in the treatment of cardiovascular diseases among others [16]. However, scientific evidence for its traditional use in cardiovascular conditions is not yet elucidated. Thus, the objectives of this work are to evaluate the effects of the leaves aqueous extract of *L. lanceolata* on anesthetized rabbits' blood pressure and electrocardiogram and also to screen the phytoconstituents responsible for the pharmacological effects of the extract.

## 2. Material and methods

### 2.1. Chemicals

The drugs used; Atropine (atr) and adrenaline (adr) were procured from Prolabo Chemical Company, France.

### 2.2. Plant

The plant material used was composed of the leaves of *L. lanceolata*, the plant was collected from Bouaké, a town located in central Côte d'Ivoire, and identified at the National herbarium under the voucher number 9397 of December 31, 1966 of the University Félix Houphouët-Boigny (Côte d'Ivoire).

### 2.3. Preparation of the extract

The leaves of *L. lanceolata* were cut into small pieces and dried at 45°C under shade at room temperature (20–22°C) for two weeks. These small pieces were powdered using an electric grinder (brand RETSCH, type SM 100, Haan, Germany). Subsequently, 100 g of powder of these dried leaves was weighed and macerated in one-liter distilled water for 48 hours. The extract was filtered on hydrophilic cotton and thereafter on Whatman No. 1 filter paper. A half-liter distilled water was added to the extract residue and macerated for 6 hours. This solution was also filtered. The filtrates were mixed and dried using an oven at 45°C. The powder obtained represented the macerated extract of the leaves of *L. lanceolata* (MALLA) [17].

### 2.4. Animal

The experiments were carried out on rabbits, *Oryctolagus cuniculus* (Leporidae). They were fed with standard granules for rodents and water ad libitum and kept in the animal facility of the Laboratory of Physiology, Pharmacology and Pharmacopoeia at Sciences de la Nature Unit of the Nangui Abrogoua University (Côte d'Ivoire) for two weeks at a temperature between 20°C and 22°C with a 12-hour light/dark cycle in order to regulate and harmonize their physiological states before the experiments. The average weight of the animals was 2±0.1 kg. The different experimental protocols were followed in accordance with the protocols for the protection of experimental animals of the European Council of Legislation 87/609/EEC [18].

### 2.5. Phytochemical screening

The leaf extract of *L. lanceolata* was screened for the presence of polyphenols, tannins, flavonoids, saponins, alkaloids, sterols and polyterpenes, and quinones. The methods used for that were carried out as described by Bekro *et al*. [19].

### 2.6. Direct arterial blood pressure measurement in rabbits

The method was as previously described by some authors [20]. The rabbits were anaesthetized using ethyl urethane (40%) at a dose of 1 g/kg bw. The saphenous vein was cannulated with heparinized polyvinyl tubing for intravenous injection of the extract and drugs (atropine, adrenaline). The left common carotid artery was cannulated and connected to a mercury manometer kymograph of Ludwig. Thus, the variations of the carotid blood pressure were transmitted to the mercury and recorded by a stylet on paper.

### 2.7. Registration of the global electrical activity (ECG) of the rabbit

The method was as previously described by Traoré *et al.* [21]. The electrocardiogram of the rabbits was recorded by the technique of external electrodes used in the human practices and adapted to rabbits. Briefly, the saphenous vein of the anesthetized rabbits by an intraperitoneal injection of 40% ethyl urethane (1 g/kg body weight) was intubated in order to administer the plant extract. The armpits of the anterior limbs and the groin of the posterior limbs were shaved and cleaned with 70% ethanol. After applying electrolytic dough, four electrodes were put and bound to the four sockets of the registration cable connected to the electrocardiograph (CARDIOFAX ECG-6851K, Nihon Kohden, Japan). The studied parameters such as P, QRS, T waves; PQ and QT intervals and cardiac frequency were recorded from the DIII derivation of the standards or bipolar Einthoven derivations on thermos-sensitive paper, at constant speed of 25 mm/s. MALLA was dissolved in Mac Ewen solution of the following composition (mM): NaCl 130; KCl 2.5; CaCl2 2.4; NaH2PO4 1.18; CO3NaH 11.9; MgCl2 0.24; C6H12O6 2.2 with a pH adjusted to 7.4.

### 2.8. Data analysis

The analysis of the results was performed using Graph Pad Prism 5 software (Microsoft, San Diego, California, USA). The values were given as the mean followed by the standard error on the mean (M± SEM). The difference between two values was determined by one-way analysis of variance (ANOVA1) and Student's t-test (unpaired t-test). The significance threshold was set at $p<0.05$ for the expression of the results.

## 3. Results

### 3.1. Phytochemical screening of MALLA

The phytochemical screening of MALLA, as shown in Table 1, revealed the presence of sterols et polyterpenes, saponosides, polyphenols, flavonoids, catechic tannins and alkaloids.

**Table 1** Phytochemical screening of the aqueous extract of *Lophira lanceolata*

| **Phytoconstituents** | **MALLA** |
|---|---|
| Sterols et polyterpenes | + |
| Polyphenols | + |
| Flavonoids | + |
| Saponosides | + |
| Catechic tannins | + |
| Gallic tannins | - |
| Quinone Substances | - |
| Alkaloids | + |

+ : presence ; - : absence

### 3.2. Dose-response effects of MALLA on rabbits blood pressure

The results showed that MALLA caused significant reductions ($p<0.001$) in blood pressure from 13.2 ± 2.5% to 51.0 ± 5.26% compared to reference blood pressures in rabbits, for doses ranged between 0.5 and 40 mg/kg bw with a 50% effective dose ($ED_{50}$) of 5.36 mg/kg bw (Figures 1A and 1B)

### 3.3. Effects of MALLA on the blood pressure of rabbits pre-administered with atropine (Atr)

Figures 3 and 4 showed the effect of atropine on MALLA-induced blood pressure reduction. The results indicated that in the absence of atropine, MALLA caused a hypotension representing a decrease of 48.8 ± 4.16% of the reference arterial pressure. In the presence of doses of atropine between $10^{-7}$ and $10^{-2}$ mg/kg bw, the hypotensions induced by MALLA were significantly decreased ($p<0.01$). Indeed, MALLA induced a hypotension decreased to 23.3±2.87% from baseline rabbit arterial pressures when the atropine dose of $10^{-2}$ mg/kg bw was pre-administered to rabbits. The dose of Atr ($10^{-2}$ mg/kg bw) significantly reduced the hypotension induced by the MALLA by about 60% (Figures 2A and 2B)

### 3.4. Effects of MALLA on the blood pressure of rabbits pre-administered with adrenaline (Adr)

The administration of increasing doses of MALLA, ranging from 5 to 30 mg/kg bw decreased the hypertension induced by the dose of $5.10^{-3}$ mg/kg bw of adrenaline. In fact, the hypertension, which represented 58.5 ± 2.41% of normal blood pressure, decreased significantly and represented only 25.7 ± 1.3%. It appeared from the analysis that all doses of the extract significantly reduced the hypertension induced by Adr up to 70%. However, this inhibition remained partial since the hypertension induced by adrenaline was not totally canceled by the MALLA doses in this series of experiments (Figures 3A and 3B).

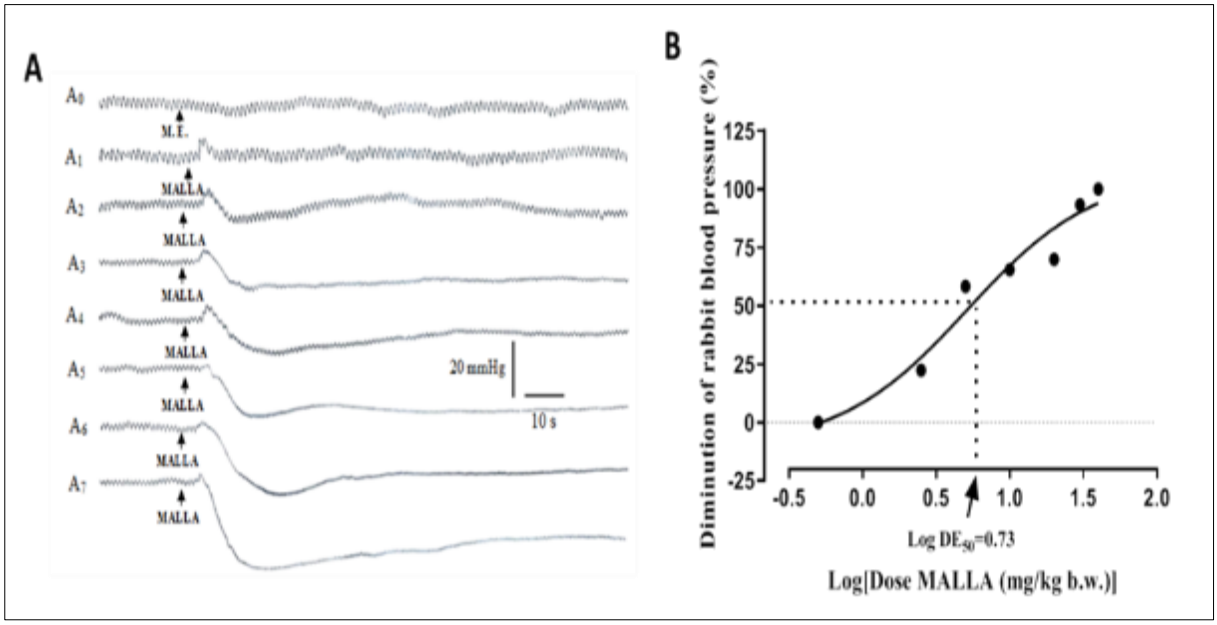


**Figure 1 (A)** Dose-response effects of MALLA on rabbit blood pressure: Control recording with M.E. ($A_0$); Effect of MALLA at 0.5 ($A_1$), 2.5 ($A_2$), 5 ($A_3$), 10 ($A_4$), 20 ($A_5$), 30 ($A_6$) and 40 ($A_7$) mg/kg bw on the rabbit's blood pressure. The arrows indicate the moment of injection of MALLA. ME: Marc Ewen solution. **(B)** Decrease in the rabbits' blood pressure induced by MALLA: The 50% effective dose ($ED_{50}$) is 5.36 mg/kg bw. **p < 0.01; ***p < 0.001: Significant difference when compared to rabbits control group blood pressure

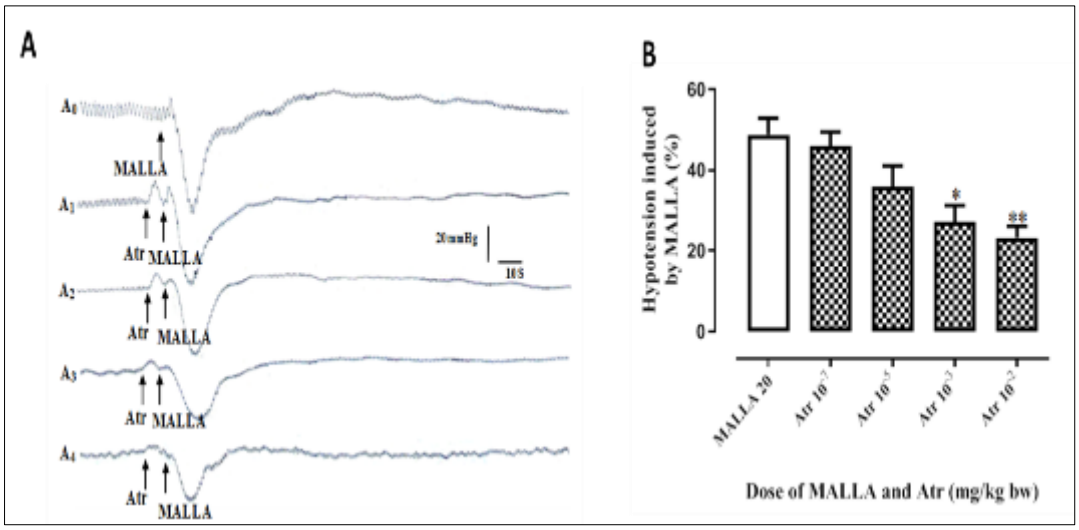


**Figure 2 (A)** Effect of MALLA on blood pressure in presence of Atr: $A_0$: Hypotensive effect of MALLA at 20 mg/kg bw; $A_1$ to $A_4$: Hypotensive effect of MALLA at 20 mg/kg bw in presence of Atr at $10^{-7}$ (A1), $10^{-5}$ (A2), $10^{-3}$ (A3) and $10^{-2}$ (A4) mg/kg bw. The arrows indicate the moment of injection of the different drugs. **(B)** Hypotension induced by MALLA in the presence of Atr: * $p<0.05$; ** $p<0.01$: Significant difference when compared to the hypotension induced by 20 mg/kg bw of MALLA

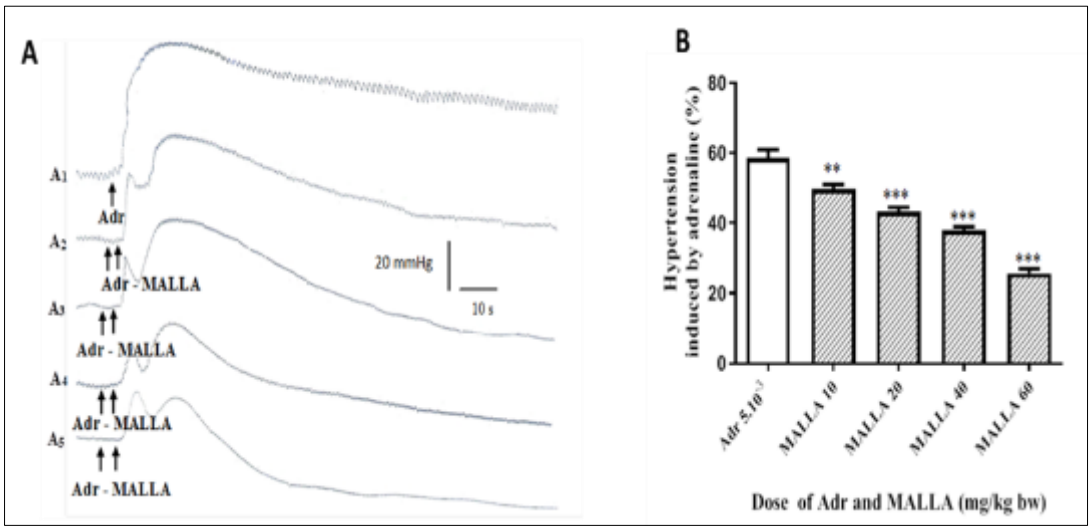


**Figure 3 (A)** Effects of MALLA on adrenaline-induced hypertension: $A_1$: Effect of adrenaline at $5.10^{-3}$ mg/kg bw; $A_2$ to $A_5$: Effect of Adr at $5.10^{-3}$ mg/kg bw (a) followed by MALLA at 5 ($A_2$), 10 ($A_3$), 20 ($A_4$), 30 ($A_5$) mg/kg bw. The arrows indicate the moment of injection of the different substances. **(B)** Antihypertensive effect of MALLA on adrenaline-induced hypertension: ** $p<0.01$ and *** $p<0.001$ Significant difference when compared to the percentage increase in blood pressure in the presence of Adr at 5.10-3 mg/kg bw, n = 4

### 3.5. Dose-response effects of MALLA on the rabbits electrocardiogram

Figures 4 and 5 are the plots of the electrocardiograms of the rabbits administered with increasing doses of the aqueous extract of *L. lanceolata* (MALLA). The plots showed general decreases in the waves and intervals of the ECG. Figures 5A, 5B and 5C showed the effects of MALLA on waves (P, QRS and T), intervals (PQ and QT) and heart rate, respectively.

The results showed that the amplitude of T, P waves and that of QRS complex were significantly reduced ($p<0.001$) to 50.7±0.61%, 7.68 ± 0.82%, 31.1± 0.59% respectively with the extract dose of 50 mg/kg bw compared to the values of on the normal ECGs of the rabbits used (Figure 5A). As for the variation of the PQ and QT intervals on the rabbits ECG at doses of MALLA varying from 0.5 to 50 mg/kg bw., the results showed a non-significant decrease ($p>0.05$) of these intervals. They were 11.36 ± 4.31% and 20.06 ± 4.28% respectively for PQ and QT intervals (Figure 5B). Figure 5C

expresses the variation in the heart rate of the rabbit treated with MALLA (from 0.5 to 50 mg/kg p.c.). A non-significant increase of 16.05 ± 3.06% in the rabbits heart rate was noted.

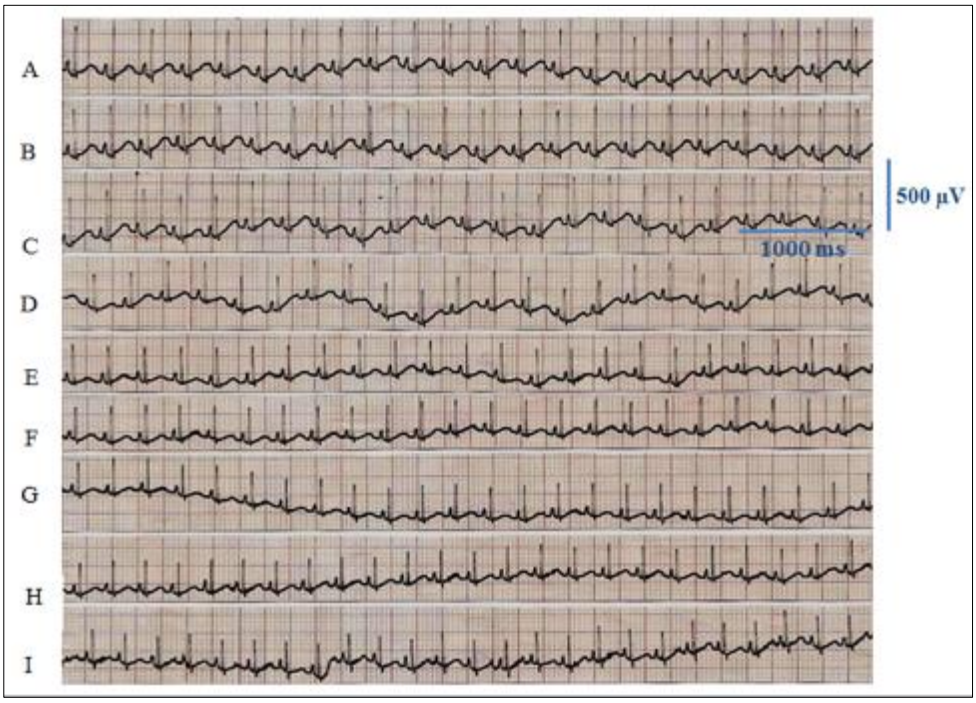


**Figure 4** Dose-response effects of MALLA on the rabbit electrocardiogram: A: Normal recording, B to I: Effect of MALLA at 0.5 (B), 2.5 (C), 5 (D), 10 (E), 20 (F), 30 (G), 40 (H) and 50 (I) mg/kg bw

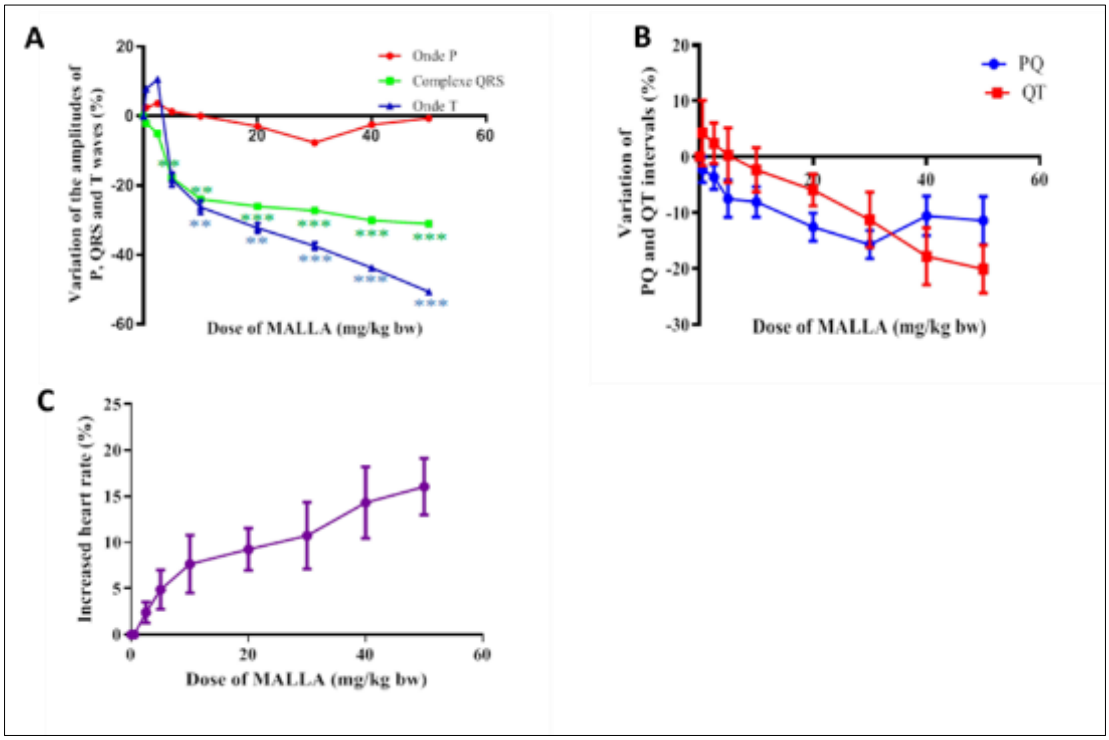


**Figure 5** Variation of P, QRS and T waves amplitudes, PQ and QT intervals and heart rate on the rabbits treated with MALLA: A: Variation of P, QRS and T wave amplitudes; B: Variation of PQ and QT intervals. C: Increase in heart rate, **p<0.01; ***p<0.001: significant difference when compared to the reference values

## 4. Discussion

The leaf aqueous extract of *L. lanceolata* (MALLA) induced a significant dose dependent hypotension in rabbits for doses ranging from 0.5 to 50 mg/kg b.w. These results are similar to those obtained by Kouakou *et al*. [22] with a decoction extract of the same plant and also with the aqueous extracts of *Mimosa invisa* and *Justicia secunda* [23,24].

The atropine pathway was hypothesized in the hypotension induced by MALLA. Thus, rabbits were pre-administered with increasing doses of atropine ($10^{-7}$ - $10^{-2}$ mg/kg b.w.). The results exhibited a significant inhibition of the hypotension induced by MALLA. This suggests that the extract contained cholinomimetic substances acting via muscarinic receptors [25]. Similar conclusions were highlighted by some researchers. Indeed, Ghayur and Gilani [26] showed that the hypotensive effect induced by an extract of *Raphanus sativus* was inhibited by atropine. Gilani *et al*. [27] reported that dried flowers 70% aqueous-methanol extract from *Lavandula stoechas* produced a drop in blood pressure in anesthetized normotensive rats abolished by atropine. The presence of acetylcholine-like phytoconstituents in the alcoholic extract of *Sesamum indicum* seeds was indicated by Nakano *et al*. [28]. Besides, some studies showed that the aqueous extract of *Desmodium styracifolium* caused hypotension mediated through cholinergic receptor stimulation in rats [29]. The actions of acetylcholine on blood pressure are well known. The intravenous injection of acetylcholine in humans or animals leads to an immediate and transient drop in blood pressure resulting from cardiac slowing and vasodilatation [22].

The slowing of the heart is explained by cell hyperpolarization following the opening of potassium channels that are directly related to G proteins [30]. The decrease in the force of contractions followed by hypotension is due to a reduction in $Ca^{2+}$ entry caused by an inhibition of adenylate cyclase and also a reduction of $Ca^{2+}$ release from sarcoplasmic stores [31]. Peripheral vasodilatation is secondary to the activation of a G protein-coupled to acetylcholine muscarinic receptors. This coupling leads to production of nitric oxide (NO) or a vasodilator substance called Endothelium Derived Hyperpolarizing Factor (EDHF), which has a relaxing effect on vascular smooth muscle [32].

The effect of MALLA was also assessed on rabbits' electrocardiogram. The results showed that the extract caused a decrease in the amplitudes of the P waves, T waves, the QRS complex, and the PQ and QT intervals. However, the heart rate was increased significantly ($p<0.001$). These effects could be due to the presence of cholinomimetic substances present in MALLA which action was found to produce a decrease in cardiac activity. Similar findings were obtained with plant extracts such as a decoction effect of *L. lanceolata* [25], and a chromatographic fraction from the aqueous leaf extract of *Bidens pilosa* [22]. These authors suggested that the inhibitory effects of the extracts were attributable to acetylcholine-like actions resulting in a depressive effect on the sinusal node and thus reducing global depolarization of other cardiac tissues. This corroborates what was observed with MALLA.

A phytochemical screening implemented with MALLA exhibited a heterogeneity of phytoconstituents composed of sterols and polyterpenes, polyphenols, flavonoids, saponins, catechin tannins and alkaloids. These substances may be responsible or involved in the blood pressure lowering effects of this extract. Indeed, many researchers demonstrated the beneficial effects of certain plant compounds on the cardiovascular system. Gilani *et al*. and Diebolt *et al*. showed that some alkaloids, saponins, polyphenols and flavonoids could be beneficial for the cardiovascular system in experimental animals [27,33]. According to Ojewole [34], tannins, polyphenols and flavonoids present in the aqueous leaf extract of *Psidium guajava* were responsible for hypoglycemic and Hypotensive effects of this plant. The positive effects of polyphenols on the cardiovascular system were largely argued by a group of scientific workers [35].

## 5. Conclusion

The effects of the leaf aqueous extract of *Lophira lanceolata* (MALLA) were investigated on rabbits' arterial blood pressure and electrocardiogram. The results showed that MALLA causes a dose dependent hypotension and a significant reduction of the global electrical activity of the rabbits' heart. This could be due to cholinomimetic substances contained in the extract.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

The authors declare no conflict of interest.

*Statement of ethical approval*

The different experiments are carried out in an ethical manner in accordance with national and international law

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