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(RESEARCH ARTICLE)

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Antihypertensive activity of *Lugwigia octovalvis* (Jacq.) P. H. Raven (Onagraceae) hydro alcoholic extract on rat

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Abstract

Our objective was to study the activity of *Ludwigia octovalvis* hydro alcoholic extract in rats made experimentally hypertensive by a hypersodic diet. After 21 days of this diet, the systolic and diastolic blood pressure of these animals increases to 200.1 ± 1.5 / 155.6 ± 1.5 mm Hg, respectively. Administered orally, the extract reduces this high blood pressure. The control group blood pressure returned to its normal value (113.2 ± 1.2/76.3 ± 1) mm Hg after 24 days, versus 9th, 15th and 19th days for animals treated with the extract at doses of 400, 200 and 100 mg / kg ($P < 0.05$). It does not have any diuretic activity but relaxes the isolated aorta contracted with norepinephrine 10^{-4} M with an EC_{50} equal to 1.18 ± 0.02 mg/ml. These results indicate that *Ludwigia octovalvis* extract has an antihypertensive activity by its vasodilator property. The polyphenols, triterpenoids and flavonoids in the extract may be responsible for its hypotensive activity.

Keywords: *Ludwigia octovalvis*; Hypertension; High-salt diet; Vasodilator

1. Introduction

Hypertension is one of the most significant causes of mortality worldwide. It is a risk factor for cardiovascular and renal complications such as stroke, heart and renal failure and diabetes [1]. Owing to the global impact of hypertension, many studies have investigated antihypertensive medications and new therapeutic alternatives [2]. Many physiological mechanisms are involved in blood pressure control including cardiac output, peripheral vascular resistance, and circulating blood volume. Various type of medications is used to take care of high blood pressure, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and calcium channel blockers, diuretics also help to reduce high blood pressure [3]. Alternative therapy such as herbal drugs also has its place as anti-hypertensive [4]. For example, in Madagascar, decoction prepared with the leaves of *Lantana camara* Linn. (Radriaka) (VERBENACEES), or *Lygodium lanceolatum* Desv. (Karakaratoloha) (CELASTRACEE), *Cajanus indicus* (Ambarivatry) (FABACEAE), *Mystroxylon aethiopicum* (Fanazava) (CELASTRACEE), *Bidens pilosa.* (Tsipolitra) (ASTERACEAE), are also used for their anti-hypertensive property [5]. Medicinal plants are empirically used as antihypertensive agents and have been reported to be effective [6].

According to the results of ethnobotany survey that we have conducted in the high plateau region of Madagascar (Antananarivo and Fianarantsoa), *Ludwigia octovalvis* (ONAGRACEAE) is used in different diseases without toxicity.

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Decoction prepared with its leaves is used as analgesic, anti-gastro duodenal ulcer, diabetes, it also helps in wound healing, high blood pressure. Based on these informations, we hypothesized that the extract of *Ludwigia octovalvis* leaves has potential antihypertensive effects. Therefore, we investigated this hypothesis in this study.

The antihypertensive effects of plants are attributed to their diuretic, vasodilator and antioxidant properties because oxidative stress is considered a risk factor in hypertension and cardiovascular diseases [7]. Reactive oxygen species (ROS) produced in all vascular cells including endothelial, smooth muscle cells play an important role in the pathophysiology of hypertension by causing vascular damage and reducing the production of nitric oxide (NO) [8].

2. Material and methods

2.1. Extraction and phytochemical screening

The leaves of *Ludwigia octovalvis* were dried in shade, and ground. The powder was macerated in a mixture of ethanol and water (60v:40v) at room temperature, during 3 days. The macerated was filtered with Wattman paper (n°1) and evaporated to dryness with a vacuum evaporator (Büchi). This extract was subject of a phytochemical screening to detect the main compounds in it [9].

2.2. Animal of experimentation

Male's rats of Wistar strain, weighing 250 to 275 g were used in this work. They were bred at the animal house of the Pharmacology and Cosmetology Laboratory of the Sciences Faculty, University of Antananarivo, with a cycle of 12/12 h of light and darkness, at a temperature of 25°C. They were fed with animal food LFL 1420 and had water *ad libitum*. The animals were fastened 18 h prior tests. Fastened animals were divided into 4 groups: 1 control and 3 treated with the extract. The extract was dissolved in water, and the animals of control group received 10 ml/kg of water by oral route, and the 3 other groups received the extract at the dose of 100, 200 and 400 mg/kg in 10 ml/kg of water orally [10].

The experiments were conducted following the guidelines of the ethic committee of Sciences Faculty, University of Antananarivo, Madagascar (Ref: 12/2021).

2.3. Induction of hypertension

All rats except the normotensive control group were placed on a high-salt diet by adding 8% sodium chloride (NaCl) to their feed for 21 days [11]. Every morning, at the same time, in a calm and warm place, systolic and diastolic blood pressure were measured in a non-invasive manner, using a tail cuff sphygmomanometer and recorded [12].

2.4. Evaluation of *Ludwigia octovalvis* extract activity on hypertension

The animals presenting high blood pressure after this period of salt loading were randomly divided into 4 groups of 6 rats each. The first group was used as control, and the extract was administered orally to the animals of the other groups, at doses 100, 200 and 400 mg/kg.

2.5. Evaluation of *Ludwigia octovalvis* extract diuretic activity

The animals were fasted 18 h prior to the test but with free access to water. After this period, they were given an oral loading of normal saline (0.9%) of 50 ml/kg of body weight. After 30 minutes, the rats were randomly divided into 4 groups of six. The animals of the first group were used as control and given 10 ml/kg of body weight of de-ionized water; while those of group 2, 3 and 4 got extract at 100, 200 and 400 mg/kg body weight in 10 ml/kg body weight. Immediately after, the rats were placed in individual metabolism cages for 24 hours. Urine was collected in a graduated cylinder and its volume was recorded [13].

2.6. Evaluation of *Ludwigia octovalvis* extract activity on vessels

Rats were sacrificed by decapitation, the thoracic aorta was isolated, cleaned of fat and connective tissue, and cut into rings of 3 mm length. The rings were suspended horizontally between two parallel stainless-steel hooks, with a basal tension of 2 g, in organ bath containing Krebs solution (NaCl 118 mM, KCl 4.7 mM, $MgSO_4$ 1.1 mM, $KH2PO_4$ 1.2 mM, CaCl2 1.5 mM, $NaHCO_3$ 25 mM, and glucose 10 mM) and bubbled with a mixture of 95% O_2 and 5% CO_2 [14]. The temperature was maintained at 37°C throughout the experiment. The isometric tension generated by the isolated aorta was measured using a force-displacement transducer (Statam Gould) and recorded with physiography (Signal Monitor®).

After 45 minutes of stabilization, orta rings (n = 6) were contracted with norepinephrine, and *Ludwigia octovalvis* hydro alcoholic extract was injected in the bath in a cumulative manner, from 0,25 mg/ml until total relaxation of the organ [15]. Dose response curve was constructed, and concentrations of *Ludwigia octovalvis* hydro alcoholic extract responsible for 50% of the relaxation (EC_{50}) were determined.

2.7. Statistical analysis

The results were presented as Mean ± SEM. The data obtained was analyzed using one way analysis of variance (ANOVA) followed by Student 't' test, and difference between means were considered significant at $p < 0.05$.

3. Results

3.1. Results of phytochemical screening

Preliminary phytochemical screening conducted on *Ludwigia octovalvis* hydro alcoholic extract revealed the presence of different secondary metabolites, such as flavonoids, tannins, polysaccharides, triterpenes, phenolic compounds, anthocyanins and saponins.

3.2. Effect of *Ludwigia octovalvis* extract on experimental high blood pressure

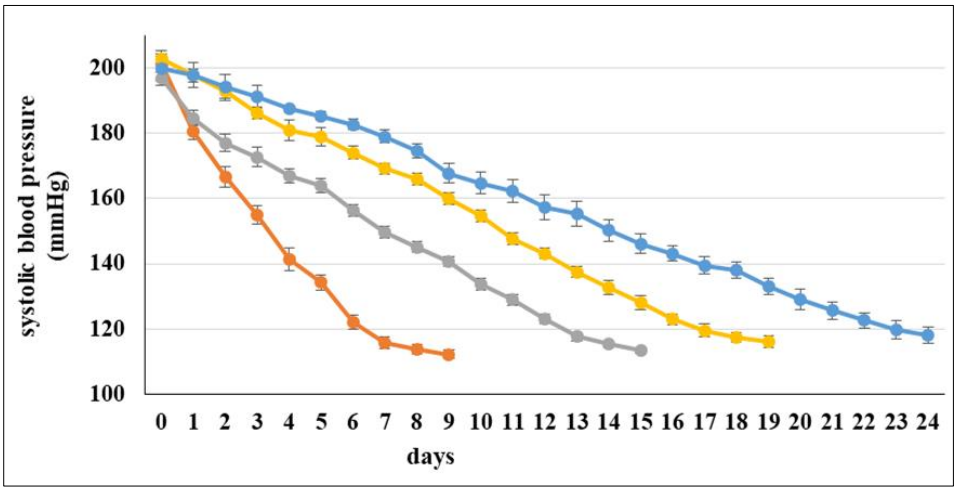

Figure 1 Systolic blood pressure variation of rats in control group and treated with the extract, administered orally, at the doses 100 , 200 and 400 mg/kg, after high salt diet induced high blood pressure ($\bar{x} \pm \bar{\sigma}$; n = 6; p<0.05)

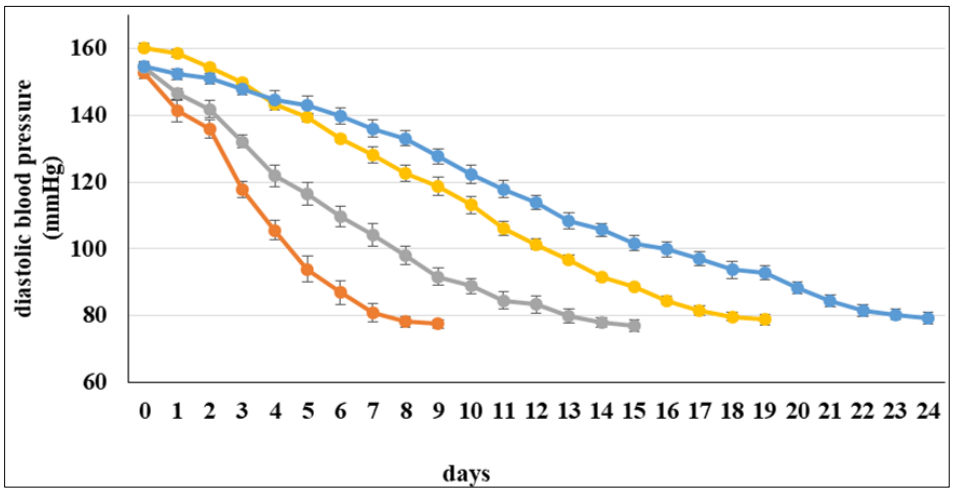

Figure 2 Diastolic blood pressure variation of rats in control group and treated with the extract, administered orally, at the doses 100 , 200 and 400 mg/kg, after high salt diet induced high blood pressure ($\bar{x} \pm \bar{\sigma}$; n = 6; p<0.05)

At the beginning of the experiment, systolic and diastolic blood pressure of the animals were 113.2 ± 1.2 mm Hg / 76.3 ± 1 mm Hg. The high salt diet increases gradually their blood pressure, which attained 200.1 ± 1.5 mm Hg/ 155.6 ± 1.5 mm Hg after 21 days. Oral administration of *Ludwigia octovalvis* extract reduces the blood pressure in a dose-dependent manner. Blood pressure return in normal value after 24 days in control group, versus 9th, 15th and 19th days for animals treated with the extract at doses of 400, 200 and 100 mg / kg ($P < 0.05$) (Figures 1 and 2). These results indicate anti-hypertensive activity of *Ludwigia octovalvis* hydro alcoholic extract.

3.3. Effect of *Ludwigia octovalvis* extract on diuresis

Administered orally, *Ludwigia octovalvis* hydro alcoholic extract does not affect the diuresis. The 24 h urine volume of control group is equal to 21.9 ± 0.9 ml, versus 20.25 ± 1, 19.8 ± 0.8, and 22.03 ± 0.9 ml in animals treated with the extract at the doses of 100, 200 and 400 mg/kg ($P > 0.05$). These results demonstrate that *Ludwigia octovalvis* hydro alcoholic extract does not have any diuretic activity.

3.4. Effect of Ludwigia octovalvis extract on contracted isolated aorta

Injected in a cumulative manner, in the bath containing isolated aorta contracted with norepinephrine at a concentration of 10^{-3}M, *Ludwigia octovalvis* relaxes the organ in a concentration dependent manner. In the absence of the extract, the maximal contraction is equal to 0,75 ± 0,02 g, which is considered as 100%. Injected in the bath it completely relaxes the precontracted organ, with CE50 of 1.18 ± 0.02 mg/ml ($P < 0.05$) (Figure 3). These results indicate the vasorelaxant activity of *Ludwigia octovalvis* hydro alcoholic extract.

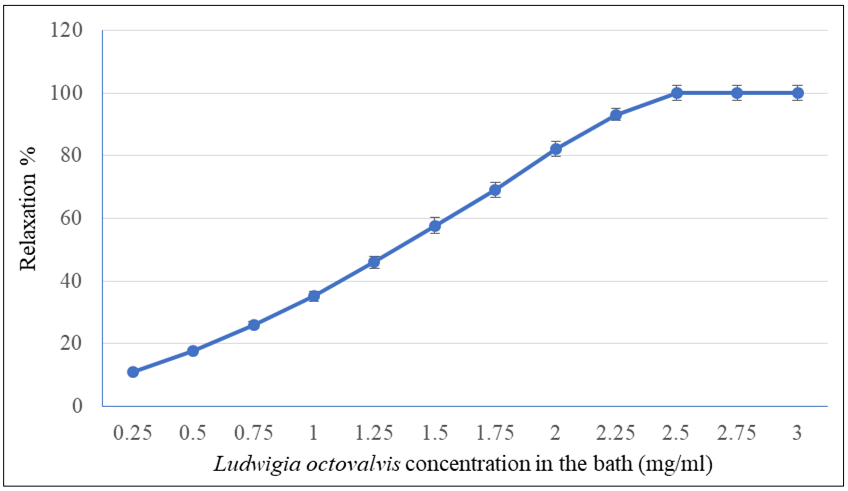

Figure 3 Variation of relaxation of precontracted isolated aorta with norepinephrine at 10^{-3}M in the bath in the presence of *Ludwigia octovalvis* injected in the bath in a cumulative manner ($\bar{x} \pm \bar{\sigma}$; n = 6; $p<0.05$)

4. Discussion

Arterial hypertension is a persistent elevation of systemic blood pressure, which is the product of cardiac output and total peripheral vascular resistance. Its pathogenesis is multifactorial and involves the interaction of multiple organs and numerous mechanisms of independent or interdependent pathways. Several mechanisms are responsible for installing high blood pressure, including increasing of cardiac output and peripheral resistance. Its treatment is based on the use of direct vasodilators or calcium channel blockers which decrease peripheral vascular resistance, or beta-blockers which reduces cardiac output or diuretics to decrease the volemia [16].

Medicinal plants also bring their contribution in the treatment of hypertension in different parts of the world [17]. *Ludwigia octovalvis* is used to treat different diseases in alternative medicine, including high blood pressure. This work is the first bioactivity-guided approach to investigate its antihypertensive activity. As increased dietary salt intake is one of the factors that play an important role in the pathogenesis of hypertension, to enable us carrying out the work, hypertension was experimentally provoked in rat with high salt diet. [18].

Following oral administration of various doses of *Ludwigia octovalvis*, systolic and diastolic blood pressure significantly decrease. The results exhibit a significant dose dependent activity in lowering blood pressure *in vivo*, especially with the high dose of the extract (400 mg/kg). These results confirm the antihypertensive effects of *Ludwigia octovalvis*

claimed in its folkloric use. Since kidneys are contributing in hypertension regulation, that is why, we have investigated the extract effect on diuresis and the disease. The results of this test indicate that it does not affect the urinary output. Since it does not have any diuretic activity, its antihypertensive activity could be due to its action on peripheral resistance, because vasorelaxation is an important mechanism in lowering blood pressure as it decreases systemic vascular resistance [19].

According to the i*n vitro* tests results that we obtained, *Ludwigia octovalvis* exhibits a significant concentration-dependent relaxation of isolated rat aorta rings precontracted with norepinephrine. It means that this extract possesses a vasodilatory activity. Hydro alcoholic extract of this plant shows dose dependent activity in lowering blood pressure *in vivo*, and vasodilation *in vitro.* Both findings suggest that its antihypertensive effects might be due to its vasorelaxation activities which lead to a reduction in the peripheral resistance, and consequently lower diastolic and systolic blood pressure. Flavonoids that it contains might be responsible for its antihypertensive activity, since flavonoids inhibit the protein kinase C, or the cyclic nucleotide phosphodiesterases or decreased Ca^{2+} uptake, contributing to their vasodilatory effects [20]. Polyphenols also play major role in this vasodilation activity of *Ludwigia octovalvis* extract since they increase in NO from endothelial cells [21]. It is also possible that terpenoids in this extract inhibit calcium channels to reduce Ca^{2+} influx and Ca^{2+} intra reticulum sarcoplasmic release, resulting to vasodilation after injecting the extract in the bath contain aorta contracted with norepinephrine [22]. As there are a load of secondary metabolites, it is difficult to give the exact mechanism of action. In perspective, we are going to identify the molecule responsible for this vasodilation activity, and its mechanism of action.

5. Conclusion

These findings showed that *Ludwigia octovalvis* hydro alcoholic extract possesses antihypertensive effects. They provide a quantitative basis to explain the traditional folkloric use of *Ludwigia octovalvis* as antihypertensive agent in Malagasy population. Its activity might be due to the polyphenols that it contains. Further investigation is necessary to know with precision its mechanism of action.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

The experiments were conducted following the guidelines of the ethic committee of the Sciences Faculty, University of Antananarivo, Madagascar (Ref: 17/2021).

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