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(RESEARCH ARTICLE)

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Evaluation of anti-hypertensive and vasorelaxant activity of ethanolic extract of *Passiflora edulis* (Passifloraceae) Leaves in rat

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Abstract

Despite the great development in the field of medicine, medicinal plants are still used in Madagascar for primary health care and claimed to be efficient. This work aimed to evaluate *Passiflora edulis* leaves ethanolic extract effect on sodium enriched diet induced hypertension in rat. After 21 days of hyper sodium diet the blood pressure increases from 118.56 ± 2.18 / 70.31 ± 1 mmHg (PAS/PAD) to 210.50 ± 2.96/ 145.88 ± 1.20 mmHg. Administered orally at doses 75, 150 and 300 mg/kg, once a day, the extract decreases the blood pressure to its normal value within 8, 6 and 4 days, versus 10 days in control group. It increases 24 h urinary volume from 3.3 ± 0.20 ml in the control animals, to 4.56 ± 0.34, 5.7 ± 0.10 and 7.96 ± 0.37 ml ($p<0.05$). It also relaxes the isolated aorta contracted with noradrenaline at 10-3M, with EC50 equal to 1.84 ± 0.03 mg/ml. These results show the anti-hypertensive effect of *Passiflora edulis* ethanolic extract, which is probably associated with its diuretic and vasorelaxation activities.

Keywords: Antihypertension; Diuretic; *Passiflora edulis*; Vasodilation

1. Introduction

Hypertension is common but can be serious due to complications it causes, if not treated. Untreated on time, high blood pressure raises the risk of cardiovascular diseases and organ damage. It is one of the most common causes of morbidity and premature death worldwide, with more than 17.9 million deaths in 2019 representing 32% of all global deaths, where 85% were due to heart attack and stroke. It can be controlled by diuretics and vasorelaxants which decrease peripheral resistance and blood flow. However, less than half of adults (42%) with high blood pressure are diagnosed and correctly treated [1]. More than three quarters of people with high blood pressure live in countries with low or medium income. The major concerns that often delay treatment allude to high costs of antihypertensive drugs, their non-availability and non-accessibility, especially for those living in rural areas. Therefore, they seek alternative approaches such as herbal remedies to treat hypertension and other diseases. In most places in Madagascar, medicinal plants are used due to their accessibility and affordability. According to ethnobotanical surveys that we have conducted in the high plateau region of Madagascar, leaves and fruits of *Passiflora edulis* (PASSIFLORACEAE) are widely used to treat hypertension. Carbal *et al.* (2021) and Garcia *et al.* (2022) have reported hypotensive and vasorelaxation activity of *Passiflora edulis* fruit. Although the hypotensive activity of *Passiflora edulis* fruit has been reported, there is no study on the antihypertensive and vasorelaxant activities of the leaves of this plant so far [2,3]. By virtue of the widespread use in traditional medicine of *Passiflora edulis* leaves decoction to treat hypertension in Madagascar, this study aimed

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to evaluate the possible hypotensive activity of its hydroalcoholic extract. It was conducted using experimentally high salt diet induced conscious hypertensive rats, and its diuretic and vascular activity mechanisms were also investigated.

2. Materials and methods

2.1. Chemicals

Norepinephrine and acetylcholine were purchased from Sigma-Aldrich Company (St Louis, Mo, USA). All chemical substances were of analytical quality.

2.2. Animals

Wistar rats of either sex, age 8-10 months, weighing 200-300 g, were used in this work. They were kept in the animal house of the Laboratory of Pharmacology and Cosmetology, Faculty of Sciences, University of Antananarivo, Madagascar. Animals were maintained under standard laboratory conditions with a natural luminosity cycle, with free access to normal animal feed and tap water. Prior authorization for the use of laboratory animals in this study was gotten from the Sciences Faculty Ethical Committee (Reg. N° ECFS-0124/009)

2.3. Preparation of the extract

Passiflora edulis leaves were collected in the Vakinankaratra region (Madagascar). A voucher specimen was deposited at the Herbarium of the Flora Department of Botanical and Zoological Park of Tsimbazaza (Antananarivo, Madagascar). The leaves were macerated in a solvent ethanol-water (60:40) at room temperature for 3 days. The extract was then filtered through Whatman qualitative grade 1 filter paper, and filtrate was centrifuged at 3000 rpm for 10 minutes. The supernatant was concentrated in a rotary evaporator, under reduced pressure.

2.4. Antihypertensive study

Before the experiment, the animals were trained to the experimental conditions by measuring their blood pressure once a day for a week. The rats were placed in an animal restrainer on a heating pad at 37 °C, and the tail was inserted in the occlusion cuff for the blood pressure reading. After this period, hypertension was induced in rats by adding 8% NaCl in their food for 21 days. Twenty-four high salt-loaded rats were divided randomly into 4 groups of per group; negative control (10 mL/kg/day distilled water), 3 groups treated with *P. edulis* leaves ethanolic extract, at doses 75, 150 and 300 mg/kg by oral route. During this experimental period, before the extract administration, systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were assessed *in vivo* every morning, in a calm environment, by the non-invasive method using tail cuff method [4].

2.5. Evaluation of *Passiflora edulis leaves* extract on diuresis

Animals were subjected to fasting overnight with free access to water. Rats were randomly assigned into four groups of six animals per group, they all received an oral water overload of 50 mL/kg. Afterwards, animals of control group were treated orally with the vehicle used for reconstitution (10 mL/kg distilled water) and the three groups received 10 ml/kg of extract at doses 75, 150 and 300 mg/kg. Dose selection was based on data obtained from preliminary tests. Immediately after oral administration of products, rats were placed in individual metabolic cages, 24 h urine was collected, and its volume was measured [5].

2.6. Vasorelaxation study

Vasorelaxant effect of *Passiflora edulis* leaves ethanolic extract was explored on isolated thoracic aortic rings preparation with intact endothelium precontracted with norepinephrine as described by [6]. The rat was euthanized by intramuscular injection of 100 mg/kg of phenobarbital, and exsanguinated. After a laparotomy, the aorta was carefully taken out and placed in Krebs's Physiological Solution (consisting of 118 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 1.2 mM $MgSO_4$, 10 mM glucose, and 2 mM $CaCl_2$), aerated with carbogen (95% oxygen and 5% carbon dioxide), at room temperature. The aorta was cleaned of the connective tissues and cut into 3–5 mm long aortic rings. These rings were hanged up at a basal tension of 1 g, in an isolated organ bath containing Krebs solution being continuously ventilated with carbogen gas at 37 °C. The aortic ring with intact endothelium was suspended between two S-shaped stainless-steel hooks in isolated organ bath, and was allowed to equilibrate for 45 min during which the solution in the bath was renewed every 15 min. The aortic rings were subjected to a viability test by exposure to 1 µM of phenylephrine prior to the execution of the experimental protocol. Integrity of the endothelium was assessed by more than 90% relaxation induced by acetylcholine (1 µM) to norepinephrine (1 µM) precontracted rings. Isometric contraction and relaxation were recorded using force displacement transducer. The transducer signals were displayed

and stored on a computer for further analysis. The responses (in grams) were displayed using (SIGNAL Monitor®). The vasorelaxant effects of the extract added cumulatively (0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 mg/mL) to norepinephrine-precontracted aortic rings were determined. Percentage of vasorelaxation was measured using the formula

$$\% \text{ relaxation} = \frac{Tt}{Tc}$$

Where
Tc = gm contraction of aortic rings with norepinephrine (1 µM) and
Tt = gm relaxation of aortic rings with extract.

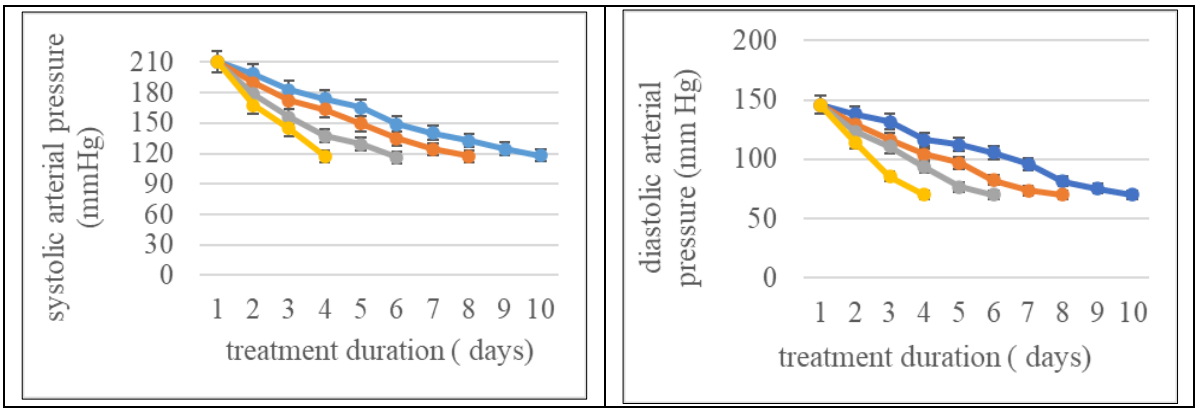
2.7. Statistical analysis

The results are expressed as means ± standard error of mean (SEM) and statistically analysed using one way ANOVA and two-way ANOVA followed by Student's "t" test. The data with p values ($p < 0.05$) was considered statistically significant.

3. Results

3.1. Effect on high blood pressure

After 21 days of high sodium diet, blood pressure rises from 118.56 ± 2.18 / 70.31 ± 1 mmHg to 210.50 ± 2.96 / 145.88 ± 1.20 mmHg ($p<0.05$). Administered orally, *P. edulis* ethanolic extract reduces systolic and diastolic arterial pressures in a dose dependent manner. Systolic and diastolic arterial pressures return to their normal values after 8, 6, and 4 days for animals treated with the extract at doses 75, 150 and 300 mg/kg, versus 10 days for control group ($p<0.05$) (Figures 1 and 2). These results indicate that *P. edulis* leaves hydroalcoholic extract reduces high salt diet induced high blood pressure.



Figures 1 and 2 Systolic and diastolic arterial pressures variation in control group and animals treated with *P edulis* leaves' extract, administered orally, once a day, at doses 75 , 150, and 300 mg/kg (m ± σ; n= 6; $p < 0.05$)

3.2. Diuretic Effect of *P. edulis* leaves extract

Administered orally, *P. edulis* extract increases the 24 h urinary volume of treated rats in a dose dependant manner. Urinary volume of control group is equal to 3.3 ± 0.20 ml, versus 4.56 ± 0.34, 5.7 ± 0.10 and 7.96 ± 0.37 ml in the animals treated with the extract at doses 75, 150 and 300 mg/kg respectively ($p < 0.05$) (Figure 3). These results demonstrate the diuretic activity of *P. edulis* leaves extract.

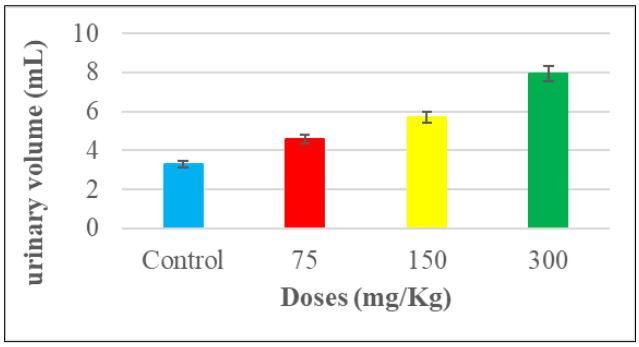


Figure 3 24 h urinary volume of animals in control group and animals treated with *P. edulis* extract, administered orally at doses 75, 150, and 300 mg/kg, after water overload of 50 ml/kg (m ± σ; n= 6; p <0.05)

3.3. Vasorelaxation Effect of *P. edulis* leaves extract

P. edulis extract was evaluated for the potency of concentration-dependent relaxations of rat thoracic aorta rings (Figure 4). The extract reduces contractile responses to aortic rings pre contracted with norepinephrine (1 µM) from 0. 5 to 4 mg/mL, added cumulatively in the bath containing the aorta ring with intact endothelium. The EC_{50} value of the vasorelaxant effect is 1.84 ± 0.03 mg/mL. These results indicate a vasodilation activity of *P edulis* leaves extract.

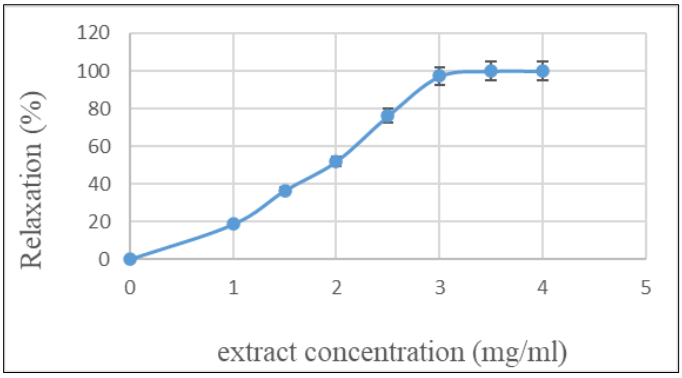


Figure 4 Effect of *P. edulis* extract, injected in the isolated organ bath in a cumulative manner, on norepinephrine-induced contraction in endothelium-intact aortic rings (m ± σ; n= 6; p < 0.05)

4. Discussion

This study aimed to validate whether the hydro alcoholic extract of *Passiflora edulis* leaves could help control high blood pressure. The results of this study indicate a drop in systolic and diastolic blood pressures to normal values within four days for the highest dose of *Passiflora edulis* leaves extract. In addition, it enhances diuresis and induces vasodilation. Even though, sodium is important in the function of organisms, its excess is a major risk for cardiovascular diseases. Meanwhile in modern society, consumption of salt is increasing in the world. Many epidemiologic, and clinical studies have confirmed that excess salt intake is an important factor in elevating the blood pressure in humans [7]. That is a reason why we investigated the effect of *P. edulis* leaves extract on rat nourished with high salt diet. After 28 days of this diet, the systolic and diastolic blood pressures of the experimental animals rise. And our results indicate that the extract reduces high salt diet induced hypertension. Within 4 days the blood pressure of the animals treated with the highest dose return to its normal value, versus 10 days for the control group. These results demonstrate that the *P. edulis* leaves extract possesses antihypertensive activity. Our findings confirm the traditional use of *P. edulis* leaves decoction to manage high blood pressure in the area where we have conducted ethnobotanical surveys. As hypertension might result from the combined effects of the vascular resistance and cardiac output, vasorelaxant medicines and diuretics are prescribed to take care of hypertension [8,9]. In this study, we have investigated the vasodilating effect of the extract and its diuretic activity to contribute to the health care system in the region where we have done the ethnobotanical survey. As all monogenic forms of hypertension have sodium retention as the main mechanism of the increase in blood pressure, increasing urinary sodium excretion is a logical and fundamental part of treatment of hypertension. Guidelines throughout the world list diuretics as one of the first-line treatments for patients with essential hypertension. This choice is based on the observation that a wide range of patients can benefit from diuretics, which counter the

extracellular volume expansion, and the salt retention associated with hypertension and reduce morbidity and mortality [10]. The results of the evaluation of the diuretic effect of *P. edulis* leaves extract exhibited a dose-dependent increase in urine output, which demonstrates its diuretic activity. This activity leads to reduction in heart output and the hypertension. Our results indicate that hydro alcoholic extract of *P. edulis* leaves relaxes the thoracic aorta contracted with norepinephrine. This vasorelaxant effect may make the greatest contribution to the reduction in high blood pressure, because vasorelaxation leads to reduction of peripheral resistance, resulting in lowering the high blood pressure. We have used high salt diet to induce hypertension, as this diet affects the endothelium leading to reduction of the release of vasodilating endothelium dependent agents. Secondary metabolites of herbs and spices, such as *Allium sativum* and *Camellia sinensis,* exhibit vasorelaxant effects by their antioxidant activity and increases in NO [11,12,13]. Literatures have reported the presence of flavonoids in *P. edulis*, and referring to those data, one can advance a hypothesis that the vasodilating effect of *P. edulis* extract could be due to the antioxidant activity of the phenolic compounds and flavonoids in the extract which protects the endothelial cells. In addition, flavonoids could also be responsible for its diuretic activity [14]. Interestingly, flavonoids have both diuretic and vasodilating activities. To sum up, this study provides evidence that the hydroalcoholic extract of *P. edulis* leaves possesses antihypertensive activity by reducing cardiac output and vascular resistance. This justifies the traditional use of its leaves decoction to take care of hypertension. However, since our study is *in vitro* and preclinical, for the security of the users, there is a need for more in-depth research and clinical trials to understand the potential of this extract and elucidate its mechanism of action.

5. Conclusion

These findings demonstrated that the ethanolic extract of *Passiflora edulis* leaves reduces high salt diet induced hypertension in rat. The blood pressure of those experimental animals returns to its normal value in 4 days with the highest dose. Il also induces vasorelaxant and diuretic effects. The diuretic effect combined to the vasorelaxant effect of this plant would explain its antihypertensive activity.

Compliance with ethical standards

Disclosure of conflict of interest

The authors report no conflicts of interest for this work.

Statement of ethical approval

The experiments were conducted following the guidelines of the ethics committee of the Sciences Faculty, University of Antananarivo, Madagascar (Reg. N° ECFS-0124/009).

Author Contributions

All authors made a significant contribution to the conception and design of the study, execution, acquisition, analysis, and interpretation of data.

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