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Evaluation of antihypertensive activity of the hydroalcoholic extract of *Sechium edule* (Jacq.) SW. (CUCURBITACEAE) fruit in rat

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Abstract

Different parts of *Sechium edule* (Jacq.) SW. have been used traditionally for the treatment of hypertension in Madagascar. This study investigated the antihypertensive effect of its fruit *in vivo* and *in vitro*. High sodium diet-induced hypertension models were used. Treatment was performed by oral administration of hydro alcoholic extract at doses 100, 200 and 400 mg/kg daily. Blood pressure was measured by non-invasive blood pressure measurement technique. After 21 days of high sodium diet, blood pressure rose from 127 ± 4.2 / 78 ± 2.3 mmHg to 212 ± 2.0 / 148 ± 1.03 mmHg ($p<0.05$). It returns to its normal value on the 6th, 12th and 15th day of treatment with the extract at doses 100, 200 and 400 mg/kg respectively. The extract increases diuresis from 3.7 ± 0.4 ml in the control group to 5.2 ± 0.2, 7.3 ± 2.3 and 8.4 ± 2.4 ml in the groups treated with the extract at doses 100, 200 and 400 mg/kg respectively ($p<0.05$). It also relaxes isolated aorta pre-contracted with norepinephrine at concentration of 10^{-4} M with EC_{50} of 1.05 mg/ml.

Keywords: *Sechium edule*; Antihypertension; Diuretic; Vasorelaxant

1. Introduction

Hypertension is one of the main causes of morbidity and mortality associated with cardiovascular diseases and is indeed a major public health issue in developed as well as developing countries, responsible for around 16.5% of annual deaths worldwide [1]. It is reported to be the fourth contributor to premature deaths because if it is not detected and controlled, it can lead to heart and kidney diseases or failures, loss of vision and atherosclerosis [2]. Essential hypertension is the main reason for hypertension and has multi factorial and overly complex pathogenesis which might be caused by increase in sympathetic nervous system activity, production of sodium-retaining hormones and vasoconstrictors, or in deficiencies of vasodilators such as prostacyclin and nitric oxide, inappropriate or increased renin secretion resulting in increased angiotensin-II production or in genetic predisposition [3,4]. While secondary hypertension prevalence is relatively low and has identifiable causes such as renovascular or endocrinological disorders [5,6].

The main classes of antihypertensives include diuretics, vasodilators such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, and beta blockers. Generally, the combination of diuretics such as thiazide or thiazide-like and vasodilators such as calcium channel blockers is recommended as initial pharmacological therapy [7,8].

Even though, pharmaceutical products are available, herbal medicines are being used in developing countries for primary health care purposes because of better cultural acceptability, inexpensiveness, considered to be potent, and have lesser side effects [9]. Symptoms that people know of high blood pressure are headaches, stiffed neck, fatigue,

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blurry vision, nosebleeds, ringing in ears and dizziness. Medicinal plants have been reported to be useful in resolving those symptoms worldwide and have been used empirically as antihypertensive [10,11].

According to an ethnobotanical survey that we have conducted in the northern region of Madagascar, the fruit of *Sechium edule* is used locally to manage those symptoms of hypertension, and we have advanced a hypothesis that it could manage this pathology. In the present work, we have investigated the antihypertensive activity of *Sechium edule* fruit hydro alcoholic extract in high sodium diet induced hypertensive models in rat as well as its diuretic and vasodilation activities.

2. Materials and method

2.1. Preparation of the extract

Fruits of *Sechium edule* were collected from the northern region of Madagascar in March 2024. They were sliced and dried under shade, in a well aerated room, at room temperature for 2 months. The dried fruit was ground to powder and the powder obtained was macerated in an ethanol-water solvent (60:40) (v:v), at room temperature for 72 hours. The macerate was filtered, and the filtrate was centrifuged at 3000 rpm for 15 minutes. The supernatant was recuperated and evaporated under pressure, using a rotavapor Evapotec®. The extraction yield was calculated.

2.2. Phyto screening

Phytoscreening was performed to detect the principal secondary metabolites in the extract according to the technique described by Fong *et al*. in 1977. This test is based on using specific reagents for each metabolite, positive reaction is characterized by precipitation or changing coloration [12].

2.3. Experimental Animals

Wistar rats of both sex of 8 months old, weighing between 200 and 260 g were used. They were bred in the animal house of the laboratory of pharmacology at the Sciences Faculty of University of Antananarivo, Madagascar under standard conditions: temperature around 20°C, dark/light cycle of 12/12 hours; they were fed with animal feed LFL 1420® and had free access of water.

2.4. Evaluation of anti-hypertensive effect of *Sechium edule* fruit extract

Hypertension was experimentally induced in rat with high salt diet at 8 % for 28 days. After this period, animals were divided into 4 groups of 6 animals per group: one group served as control, and three treated with the extract. Their blood pressure was measured every morning before feeding them, and the extract was administered orally at doses 100, 200 and 400 mg/kg in 10 ml/kg of distilled water [13,14].

2.5. Evaluation of *Sechium edule* fruit extract effect on diuresis

Diuretic activity of the extract was evaluated on its effect on 24 h diuresis. The animals were deprived of food for 12 hours. All the animals were given water overload of 50 ml/kg by oral route, and 30 minutes later, they were divided into 4 groups of 6 rats per group, one served as control and three treated with the extract at doses 100, 200 and 400 mg/kg, administered orally in 10 ml/kg of distilled water. Immediately after drug administration, the animals were put individually in metabolism cages. The diuretic activity was determined by measuring parameters such as time to the first urination, urinary volume [15,16].

2.6. Evaluation of *Sechium edule* fruit extract effect on isolated aorta

On the day of the functional experiment, the animal was euthanized by injecting intramuscular 100 mg/kg of phenobarbital. It was exsanguinated and a thoracotomy was performed; the thoracic aorta was removed, cleaned of adhering connective tissue, and cut into 5 mm length rings. They were mounted in organ bath filled with Krebs–Henseleit solution maintained at 37°C and aerated with 95% O2, 5% CO2, under a resting tension of 1.5 g. Each aortic ring was allowed to equilibrate for 60 min, during which the solution in the bath was renewed every 10 minutes. After this period, 10 µM of norepinephrine was injected in the bath to test the organ viability and to sensibilize the organ. At the maximum contraction, endothelium viability was confirmed by a relaxant effect of acetylcholine injected in the bath with final concentration of 10 µM. Only rings that showed a relaxation higher than 50% of the noradrenaline-induced precontraction were used. The tissue was then washed every 10 min for 30 min. after this period, the organ was then contracted with norepinephrine injected in the bath in cumulative manner to get final concentration of 10^{-9} M until maximal contraction. At plateau of contraction, the extract was injected in the bath in a cumulative manner, and

concentration-response curve was established. The relaxation of each concentration was calculated as a percentage of the correspondent stable noradrenaline-induced precontraction (Emax or maximum effect) and EC_{50} values (concentration of the extract causing 50% of the maximum response) were calculated from the linear part of the curve, using Microsoft Excel 2019 for Windows.

2.7. Expression and analysis of results

All the values were expressed as mean ± standard error of the mean ($\bar{x}$ ± s.e.m). Statistical analysis was preformed using one-way ANOVA followed by Student's 't' test, p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Extraction and Phyto screening results

Maceration of 200 g of dry fruit powder in ethanol-water (60:40) at room temperature for 72 hours gives 32.64 g of dry extract, which corresponds to 16.32% of extraction yield. Phyto screening performed on this extract revealed the presence of high quantity of phenolic compounds and alkaloids, mild quantity of flavonoids, steroids and triterpenes while saponins and glycosides are present in low quantity in the extract.

3.2. Effect of *Sechium edule* extract on hypertension

Administered orally, once a day, at doses 100, 200 and 400 mg/kg, the hydro alcoholic extract of *Sechium edule* fruit reduces high sodium diet induced hypertension. Before this diet, the normal blood pressure value was 127 ± 4.2/78 ± 2.3 mmHg. After 21 days of the high salt diet, it increases to 212 ± 2/148 ±1 mmHg ($p<0.05$). Blood pressure of animals treated with the extract return to its normal value in a dose dependent manner in comparison with the control group which remains high during the test.

On the 18th day, the control group blood pressure remains high at 204 ± 1.2/ 126 ± 0.5 mmHg, while it returns to its normal value on the 6th, 12th and 15th day for animals treated with the extract at 100, 200 and 400 mg/kg which are respectively 126.5 ± 2.5/82 ± 4.9, 124 ± 1.45/ 83± 2.33 and 123.66 ± 4.04 /81 ± 1.91 mmHg ($p<0.05$) (Figures 1 and 2). These results indicate the anti-hypertensive activity of the hydro alcoholic extract of *Sechium edule* fruit.

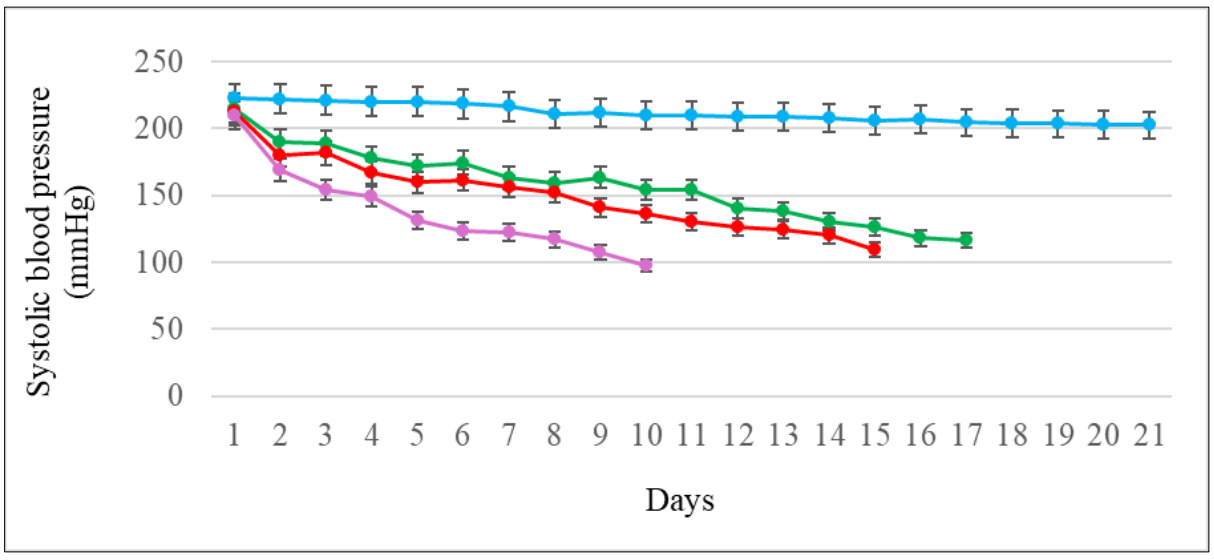

Figure 1 Variation of arterial systolic pressure of control group with high salt diet induced hypertension ( ) and animals treated with the extract, administered orally once a day, at doses 100 ( ), 200 ( ) and 400 mg/kg ( ) ($\bar{x}$±s.e.m; n =10; $p < 0,05$)

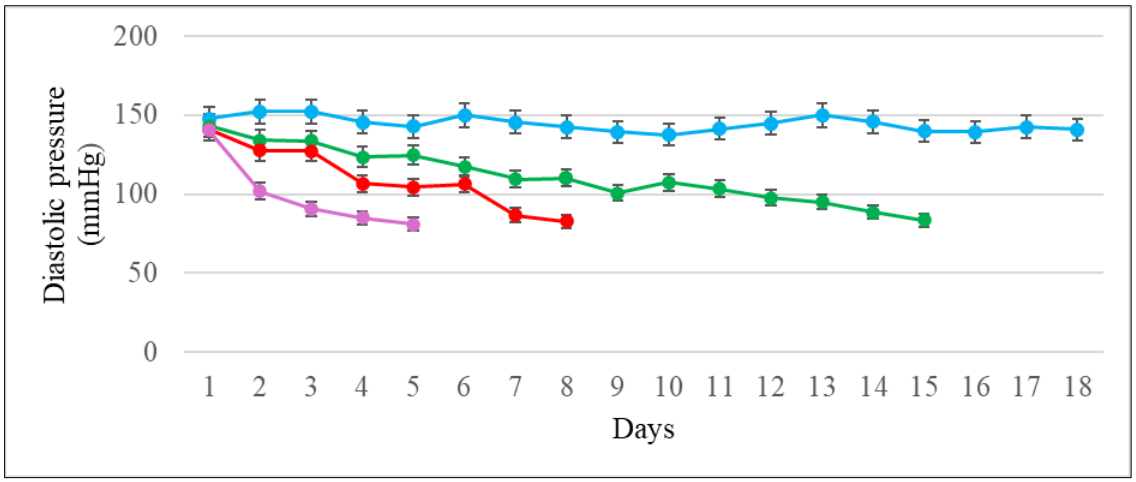

Figure 2 Variation of arterial diastolic pressure of control group with high salt diet induced hypertension ( ) and animals treated with the extract, administered orally once a day, at doses 100 ( ), 200 ( ) and 400 mg/kg ( ) ($\bar{x}$±s.e.m; n = 10; p < 0,05)

3.3. Effect of *Sechium edule* extract on urinary output

The hydro alcoholic extract of *Sechium edule* fruit increases diuresis in a dose-dependent manner in the treated group as compared to the control group. The extract at doses 100, 200 and 400 mg/kg produced significant diuresis of 5.2 ± 0.2, 7.3 ± 2.3 and 8.4 ± 2.4 ml respectively, versus 3.7 ± 0.4 ml in the control group ($p<0.05$) (Figure 3). These results indicate the diuretic activity of the extract.

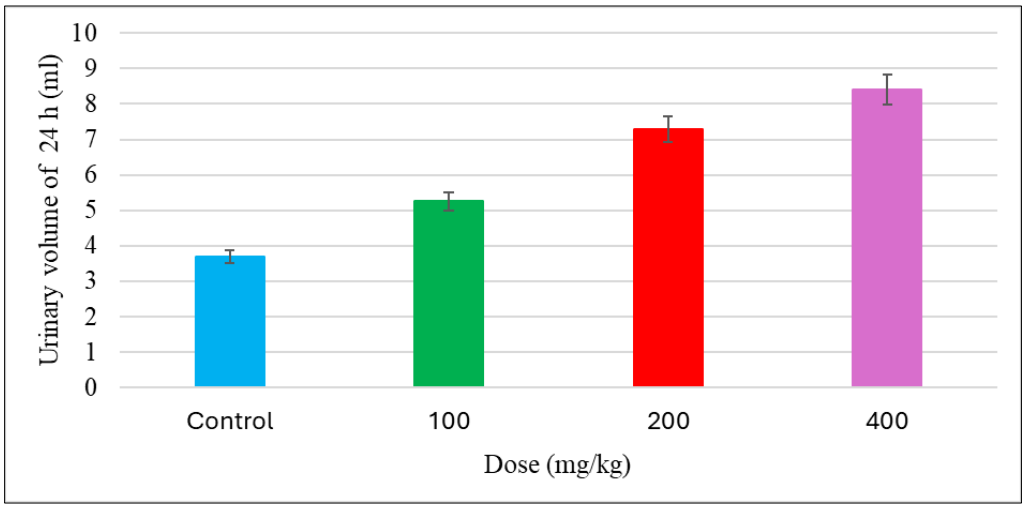

Figure 3 Variation of 24 h urinary volume of control group ( ) and treated with the extract, administered orally at doses 100 ( ), 200 ( ) and 400 mg/kg ( ), after water overload of 50 ml/kg ($\bar{x}$ ± s.e.m.; n =10; $p<0.05$)

3.4. Vasorelaxant effect of *Sechium edule* fruit extract

Added cumulatively in the bath containing the isolated aorta pre-contracted with norepinephrine at 10^{-4} M, the extract relaxes the organ in a concentration dependent manner. It started relaxing the organ at concentration 0.2 mg/ml and relaxes it completely at concentration of 2 mg/ml, with EC_{50} of 1.05 mg/ml (Figure 4). These results indicate the vasorelaxation activity of hydro alcoholic extract of *S. edule* fruit.

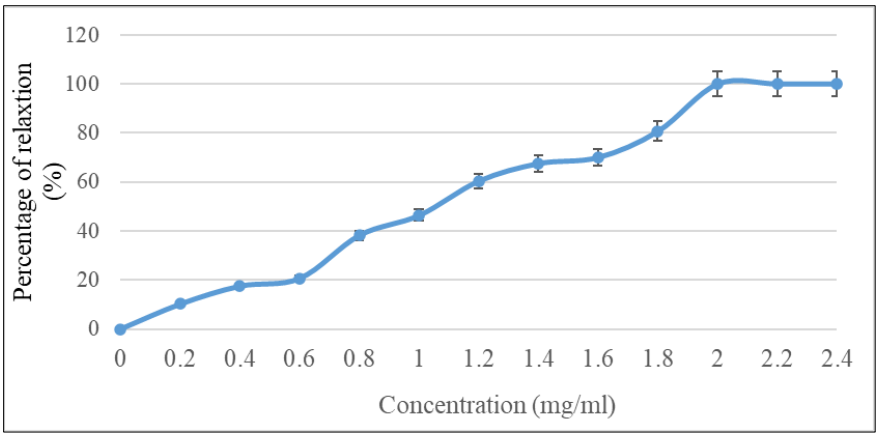

Figure 4 Variation of relaxation of isolated aorta contracted with norepinephrine at concentration of 10^{-4} M in the presence of hydro alcoholic extract of *S. edule* fruit, injected in the bath in a cumulative manner ($\bar{x}$ ± s.e.m; n =10; p < 0.05)

4. Discussion

The current investigation represents the first effort to describe the effect of hydro alcoholic extract of *Sechium edule* fruit, used as antihypertensive in the northern region of Madagascar. The antihypertensive activity of the extract was performed in rat with high blood pressure induced by high salt diet, because high salt intake has been associated with high blood pressure and excess salt intake produces hypertension in these animals, which mimics human hypertension [17,18]. Our results indicate that administered orally, the extract reduces the high sodium diet induced hypertension in a dose dependent manner. At the highest dose of 400 mg/ml, the blood pressure returns to its normal value within 6 days, while it remains high during the experiment period for the control group, which demonstrates the extract antihypertensive activity.

Antihypertensive drugs may be divided into two groups: those which block the renin–angiotensin system (RAS), angiotensin receptor antagonists (ARAs), direct renin inhibitors (DRIs), and β-blockers. The second group of drugs works by increasing water and sodium excretion, thereby reducing intravascular volume, or by causing vasodilation through non-RAS pathways, for example, diuretics and calcium channel blockers (CCBs) [19,20]. Since diuretics and vasodilators are the first line of medications for hypertension, the extracts' diuretic and vasorelaxant activity were evaluated in this study.

The results of the assessment of the diuretic effect of the extract indicate that it increases the 24 h urinary output in a dose dependent manner, which demonstrates its diuretic activity. The increase of water excretion reduces the blood volume and thus the blood pressure. At the same time, diuretics provoke a loss of sodium, leading to a reduction of vascular reactivity, which explains the antihypertensive activity of diuretics [21]. This diuretic activity explains partially the antihypertensive activity of the hydro alcoholic extract of *Sechium edule* fruit. There are several phytochemicals such as phenols, are responsible for diuretic effects of plants [22,23]. Since *Sechium edule* fruit hydro alcoholic extract contains this chemical group, we suggest that they might be responsible for its diuretic activity.

To investigate the direct effect of hydro alcoholic extract of *Sechium edule* fruit on the vasculature, we performed experiments using rat isolated aorta precontracted with norepinephrine. We found that this extract exerts a vasorelaxant effect in a concentration-dependent manner. It induces concentration-dependent relaxation. Since vasodilators are indicated in hypertension, this vasorelaxant effect of the extract contributes to its antihypertensive activity observed in the results of *in vivo* investigations.

Different literatures reported that high salt diet has a deleterious effect on endothelial function and leads to endothelial dysfunction, an imbalance between endothelium-derived relaxing factors, and contracting factors, favouring the latter ones [24]. Additionally, studies carried out in rodents have demonstrated that the decline in NO synthesis during high salt diet results from an increase in reactive oxygen species (ROS) [25]. Considerable evidence suggests that oxidative stress, which results in an excessive generation of ROS, plays a key role in the pathogenesis of hypertension [26]. Antioxidant therapies have been evaluated to decrease ROS production or increase their scavenging. In this line, polyphenols, are well known for their beneficial role in prevention and therapy of hypertension, by acting as free radical scavengers [27].

It has also been reported that polyphenols, with their antioxidant effect, improve endothelial dysfunction by increasing NO and prostacyclin formation leading to vasorelaxation and reduction of high blood pressure in rodents. In the current study, the antihypertensive effect of *Sechium edule* fruit may also be due to the antioxidant effect of polyphenols. This activity protects the endothelial which allows it to liberate the vasodilators such as prostacyclin or NO [28,29].

The results of phytochemical screening done on this extract revealed the presence of polyphenolic compounds. Therefore, molecules in this family might be responsible for the antihypertensive activity of this extract. It is important to mention that this extract still contains several secondary metabolites. Therefore, it is necessary to direct the attention to compounds present in organic extracts, and further investigations will provide evidence of whether its vasorelaxant activity passes through endothelium or not. For the time being, the present results provide pharmacological support for the use of *S. edule* fruit in ethnomedical practices as antihypertensive in the northern region of Madagascar.

5. Conclusion

Our study has shown for the first time that hydro alcoholic extract of *Sechium edule* fruit possesses potent diuretic and vasorelaxant effects. These results justify the use of the fruit of this plant in traditional practices as antihypertensive. Moreover, efforts will be directed to isolate the active compounds from this extract to allow us understand its mechanism(s) of action and design new therapeutic agents with potential antihypertensive effects.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declared no conflict of interest.

Statement of ethical approval

This study obtained approval from the Scientific and Ethical Review Committee of the Sciences faculty of University of Antananarivo, Antananarivo, Madagascar. The animals were treated with care throughout the study period and were kept in a well-controlled area according to the National Guidelines for the Care and Use of Laboratory Animals

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