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ANALYSIS OF POTENTIAL INTERACTIONS OF RAMIPRIL - AMBON BANANA (*Musa paradisiaca var. sapientum (L.) Kunt.*) ON HYPERKALEMIA RISK IN WHITE RATS

I Gusti Ayu Sintia Dewi[1], Ni Putu Rutin Seciolini Agristy[2], Ida Ayu Gendari[2]
Made Krisna Adi Jaya[2*]
[1]Department of Pharmacy, Faculty of Math and Science, Udayana University, Bali, Indonesia
Corresponding author email: krisnaadijaya@unud.ac.id

ABSTRACT

Introduction: Drug and food interaction is a condition in which nutritional factors present in food have a significant influence effect on drug therapy, both potentially increasing or decreasing the effect of drug therapy. Indonesian people have a habit of taking medicine by using food or drink. Bananas are the primadonna that is often consumed to speed up the swallowing process and reduce the bitter taste of medicine. It turns out that the consumption of bananas together with ACE inhibitors can increase the risk of hyperkalemia. Lack of information about the effects caused by drug and food interactions, so it is necessary to do related research. **Objective**: This study aims to determine the interaction of giving ramipril together with Ambon banana on the risk of hyperkalemia. **Methods**: A real experimental study while still adhering to the Covid'19 health protocol. White rats were divided into four groups, conditioned by hypertension, then intervened with ramipril and Ambon banana. Blood serum was taken and analyzed using UV spectrophotometry to obtain serum potassium levels. The levels obtained were analyzed using the One Way ANOVA Test. **Results**: The mean serum potassium level of the positive control group was 4.93±0.58; negative control 4.13±0.60; normal control 4.76±0.59 and treatment 5.10±0.38. The highest serum potassium level was in the ramipril treatment group together with Ambon banana, but still in the normal range of 3.60–5.50 mmol/L. One Way Anova test results ($p = 0.054$). ($p>0.05$) showed no significant difference. **Conclusion**: There is no specific increase in levels of ramipril concurrently with Ambon banana so it does not have the potential to cause the risk of hyperkalemia.

Keywords: Drug Interaction, Ramipril, Ambon Banana, Serum Potassium, Hyperkalemia

INTRODUCTION

Interaction between drugs and food is a problem that is often underestimated by the community. Drug interaction with food is a condition where the nutritional factors present in food can have a significant influence on the therapy of a drug [4]. Drug interactions can potentially increase the therapeutic effect of drugs consumed or vice versa can also reduce the therapeutic effects of drugs consumed [1].

Most people in Indonesia have the habit of taking medicine by using food or drink, for example, bananas. Banana is a primadonna fruit that is used to speed up the process of swallowing drugs and reduce the bitter taste of drugs. The types of bananas consumed are usually varied, one of which is commonly consumed by the wider community is the Ambon banana [14].

Ambon banana has a fairly high potassium content in it, which is around 487 mg/fruit [14]. Another study stated that 100 g of Ambon banana contains 435 mg

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of potassium [11]. The high content of potassium in Ambon bananas is often used by people to lower blood pressure. This is because the potassium content in Ambon banana can cause inhibition of the *Renin-Angiotensin System* (RCS), resulting in a decrease in aldosterone, which causes a decrease in sodium and water reabsorption in the kidney tubules. Then there will be an increase in diuresis so that blood volume decreases and blood pressure decreases [7].

However, the public does not know that when Ambon banana is given together with ACE inhibitor antihypertensive drugs, it can cause drug interactions. This is evidenced by several studies which state that when ACE inhibitors are taken together with high potassium supplements, they can increase potassium levels in the blood. So, if ramipril is taken together with Ambon banana, it can cause high levels of potassium in the blood. High levels of potassium can have an effect on decreasing the effect of drug therapy and increasing the risk of hyperkalemia. In addition, high levels of potassium in the blood can have an effect on the work of the heart [10].

There are still few studies that report on the effects of drug interactions with food. However, it is very important to do in order to prevent the occurrence of unwanted toxic effects. So based on these considerations, it is necessary to conduct a study that examines more deeply the interaction effects caused by the use of the antihypertensive drug ramipril together with Ambon banana.

METHODS

1. Research Design

Study of the Interaction Effect of Giving Ramipril Together with Ambon Banana (*Musa paradisiaca var. sapientum (L.) Kunt*.) Against the Risk of Hyperkalemia in White Rats was carried out with an experimental research design. This research was carried out while still complying with the Covid'19 health protocol.

2. Location and Time of Research

The research was carried out at the Laboratory of Test Animals and Laboratory of Pharmaceutical Analysis, Udayana University. In total, all stages of the research, including the preparation of the journal, were carried out for four months.

3. Tools

Equipment that will be used in this research are Beaker (Pyrex), Measuring Glass (Pyrex), Hotplate, Analytical Balance (Ohaus), Scales (GSF-4405), UV Spectrophotometry (Uv mini-1240), Rat Sonde (Obsidi Medica), Microhematocrit (Vitrex), EDTA Tube, Eppendorf Tube, Mortar, Blender, Vortex Tool, and Centrifuge.

4. Materials

The materials used in this study were Ambon bananas obtained from the Sidemen Traditional Market, Karangasem. Ambon bananas were determined at LIPI BKT Eka Karya Bali Botanical Gardens with letter No. B-. 5724/III/KS.01. 03/7/2021. NaCl, Prednisone 5 mg (Eltazon), CMC Na (Aloin), Ramipril 2.5 mg (OGB Dexa), Aquadest, Banana Ambon, Rat Bio Feed, Trichloroacetic Acid, Sodium Tetraphenylboron (Tokyo Chemical Industry), and Sodium Hydroxide (Germany).

5. Procedure

A. Preparation Animals

Animals used were white male rats (*Rattus norvegicus* L.) Wistar strain 2-3 months old and weighing 100-125g obtained in Denpasar, Bali. Before being grouped, the rats were acclimatized for seven days, accompanied by observations of their body weight and physical condition. Sick mice will not be included in this study. This research has complied with the protocol and received a certificate of passing the ethical review from the Ethics

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Commission of the Faculty of Veterinary Medicine, Udayana University.

B. Hypertension Induction

Normal mice were conditioned by hypertension by being induced by using 2% NaCl solution and Prednisone in 0.5% NaCl CMC with a volume of 2 ml/200g BW orally. This process is carried out once a day for seven consecutive days.

C. Intervention Ramipril

The dose of ramipril used was 0.6 mg/kg BW. Ramipril was given to test animals that had been conditioned to hypertension at a dose of 0.6 mg/kg BW orally once a day for three consecutive days.

D. Intervention of Ramipril and Ambon Banana

The dose of ramipril used was 0.6 mg/kg BW, while the banana used with a concentration of 100% was 1 ml/day. The intervention was carried out for three consecutive days.

E. Animal Intervention Test

Animals consisted of 24 male Wistar rats, which were divided into four groups, namely:

1. Group 1 as a negative control, consisting of 6 hypertensive rats on a standard diet given a placebo.
2. Group 2, as a positive control, consisting of 6 hypertensive rats on a standard diet group, was given ramipril.
3. Group 3, as normal control, consisted of 6 rats that were given only feed, distilled water, and placebo.
4. The treatment group consisted of 6 rats with hypertension who were given a diet with ramipril along with Ambon banana.

F. Serum Sampling

Blood sampling was performed through the orbital sinus of the eye on day 10. The blood obtained was collected in the EDTA tube carefully to prevent hemolysis. The blood was centrifuged at 6000 rpm for 5 minutes to obtain a clear filtrate. This supernatant (serum) will be used for the measurement of potassium levels.

G. Determination of Potassium Levels

Potassium levels were measured using a spectrophotometer. 50 µL of serum was added to 500 µL of trichloroacetic acid, centrifuged at 6000 rpm for 5 minutes, the supernatant was obtained. The test was carried out by reacting 200 µL of the supernatant with a mixture of sodium tetraphenyl boron and 2 mL of sodium hydroxide, vortexed and allowed to stand for 5 minutes and then measured at a wavelength of 578 nm.

H. Analysis

The data was obtained from the measurement of serum potassium levels. Then the data were collected and analyzed statistically using the One Way ANOVA Test.

RESULTS

1. The results of the acclimatization of Animals

Characteristics of the weight data of rats during the 7-day acclimatization process were declared homogeneous. Acclimatization is done so that the test animals can adapt to the experimental environment—adaptation measured in the form of changes in the bodyweight of rats and observations of their physical condition. The results of measuring the weight of the rats can be seen in Table 1.

2. Serum Potassium Levels Result

Serum potassium levels of data characteristic of test animals is stated homogeneous. Of the four groups of test animals, all of them met the range of serum potassium levels. That is in the range of 3.60 - 5.50 mmol/L [12].

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Table 1. Weight Mice During the acclimatization process

Group	MiceWeight (g) (Mean ± SD)							
	Day I	Day II	Day III	Day IV	Day V	Day VI	Day VII	p
Positive Control	108.33 ± 7763	110.33 ±8238	± 6812113	113.67 ± 7005	115 ± 8438	115.17 ± 6,969	116.50 ± 6716	0504
Negative Control	103.83 ± 5,776	104.67 ± 7,230	108.17 ± 6,969	108.83 ± 6853	109 ± 6512	111.67 ± 6593	113.17 ± 6113	0182
Control Normal	109.50 ± 6,285	112.33 ± 6,743	113.33 ± 7202	115.17 ± 6,014	115.67 ± 6683	115.67 ± 6.890	117.33 ± 6683	0483
treatment of	106.83 ± 5,115	109.50 ±4,806	112 ±4,690	± 4,708112.17	112.835 ,269±	113.67 ± 5,391	115 ± 4899	0127

* Description: test One Way ANOVA, p> 0.05 were not significantly different in all groups

Table 2. Serum Potassium Levels Serum Potassium

Group	Levels (Mmol/L)			P
	Mean (mean ± sd)	Min	Max	
Positive Control	4.93±0.58	3.93	5.58	0.054
Negative Control	4.13±0.60	3.22	5.09	
Normal Control	4.76±0.59	4.15	5.91	
Treatment	5.10±0.38	4.49	5.72	

Description: One Way ANOVA Test, p > 0.05, not significantly different in all groups

Table 3. Pulse Rate Per-minute

Group	Pulse Per-minute	
	Mean (mean ± sd) Before Treatment	Average (mean ± sd) after treatment
Positive Control	158.17 ± 24.3	211 ,67 ± 31.7
Negative Control	205.67±6.10	231±4.08
Normal Control	187.17±23.4	235.17±11.3
Treatment	208.33±17.5	234.5±4, 65

The highest potassium levels were in the treatment group (the group that was given ramipril together with Ambon banana). The results of serum potassium levels can be seen in Table 2.

3. Pulse Rate Results

Results of the test animal pulse data were measured for 1 minute before treatment and after treatment. The highest average pulse rate before treatment was 208.33±17.5, while after treatment was 235.17±11.3. The normal heart rate of rats is 250-450 beats/min [8]. Compared to the reference, the pulse rate of the test animal is still fairly normal. In this study, there was an increase in all test groups before and after treatment. The results of the pulse rate can be seen in Table 3.

DISCUSSION

The test animals used in this study were white rats (*Rattus novergicus* L.) Wistar strain. Male rats were chosen as test animals because male rats do not affect the hormonal cycle, so it is hoped that in the future, it will not affect the results of the research to be carried out [9].

The test animals used were from Denpasar, Bali, aged 2-3 months, and body weight ranged from 100g-125g. It is feared that the difference in place can cause physiological and behavioral differences in

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the test animals. Therefore, before being used in research, the test animals were acclimatized for seven days. Acclimatized rats aim to observe the adaptability of rats to their new environment [2].

All groups of test animals except the normal control group, which had been acclimatized, were conditioned to hypertension first. To obtain the Wistar strain rat model, rat hypertension was induced using 2% NaCl solution and Prednisone in 0.5% NaCl CMC with a volume of 2 ml/200g BW orally once a day for seven consecutive days.

Test animals that had been conditioned to hypertension were intervened with ACE inhibitors (ramipril) or ramipril together with Ambon bananas. The treatment was given once a day for three consecutive days. The normal control group was only given feed and aquadest *ad* libitum together with placebo. The placebo given was Na CMC. It aims to avoid the bias effect caused by giving a placebo in the study.

Ramipril is an ACE inhibitor antihypertensive drug. ACE inhibitors are the class of drugs most often recommended as the first line to treat hypertension in patients <55 years old [3]. Its mechanism of action is by inhibiting the converting enzyme, peptidyl dipeptidase, which hydrolyzes angiotensin I to angiotensin II and inactivates bradykinin. Drugs of this class reduce systemic vascular resistance and mean systolic and diastolic blood pressure in various hypertensive states [13].

Consumption of ACE inhibitors in the long term can cause side effects of hyperkalemia. If the patient is in heart failure, hyperkalemia can cause heart rhythm disturbances and cardiac arrest. The use of ACE inhibitors in hypertensive patients with a history of heart failure can increase the risk of developing hyperkalemia by 2%-10% [5].

Potassium levels will increase if you get an excessive intake of potassium [5]. In 100 g of Ambon banana contains 435 mg of potassium[11]. Consumption of Ambon banana causes an increase in potassium concentration[14]. High levels of potassium can have an effect on decreasing the effect of drug therapy given and can cause hyperkalemia. In addition, high levels of potassium in the blood are very risky for people with hypertension because it will have an effect on the work of the heart [10].

Based on the results of the measurement of serum potassium levels in the blood of white rats, it showed that all treatment groups were still in the normal range of serum potassium levels in the blood. Based on the study stated that the normal range of serum potassium levels is in the range of 3.60 - 5.50 mmol/L[12]. Another study stated that serum potassium levels under normal physiological conditions in rats were in the range of 3.4 – 5.5 mmol/L. Meanwhile, if the potassium level is above 7.5 mmol/L, it causes a decrease in ventricular conduction until cardiac arrest [10].

The highest mean serum potassium level was in the treatment group. This is in accordance with the theory which states that when ACE inhibitors are taken together with high potassium supplements, it can increase potassium levels. ACE inhibitors work synergistically with bananas causing an increase in potassium levels [10].

The results with the One Way Anova stated that the P-value obtained was 0.054. The result of $P > 0.05$ stated that there was no significant difference. This means that the consumption of ramipril together with Ambon banana did not cause a significant increase in serum potassium levels in white rats so that it did not have the potential to cause the risk of hyperkalemia.

Another parameter used is the pulse rate. The results of the average pulse rate in this study showed an increase in pulse rate after the intervention was given. This is in accordance with the theory, where high potassium levels can cause vasodilation, causing a decrease in total peripheral retention resulting in increased cardiac output [11].

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CONCLUSION

Administration of ACE inhibitor class antihypertensive drugs (Ramipril) together with Ambon banana can increase the serum potassium level of rats. However, the increase in serum potassium levels was not significant and was still in the normal range so that it did not cause the risk of hyperkalemia. Giving ramipril together with bananas also has an effect on increasing the pulse rate of white rats, because high potassium levels can increase cardiac output.

CONFLICT OF INTEREST

This research was conducted independently. The author does not disclose financial or personal relationships with other people or organizations that may improperly influence the work.

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