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Effect of Dragon Fruit Juice (Hylocereus Polyrhizus) on Xanthine Oxidase Activity and Blood Nitric Oxide Levels on Rats with Hyperuricemia

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Hyperuricemia, the condition when serum uric acid level is above normal value, is not only a risk factor for the occurrence of gout, but also the incidence of cardiovascular disease. Red dragon fruit (Hylocereus polyrhyzus) are rich in flavonoids which have the potential as antihyperuricemia. This study aims to prove the effect of red dragon fruit to hyperuricemic rats on the activity of xanthine oxidase enzyme and the levels of nitric oxide (NO). The methods used is a true-experimental randomized pre-post with control group design. The hyperuricemic rats treating with broth blocks and potassium oxonate. The sample in this study consisted of thirty Wistar rats (Rattus norvegicus) were divided into 6 groups: healthy control (K0), hyperuricemic control (K1), and treatment groups (K2, K3, K4, K5). Intervention was given for 28 days with allopurinol 1.8 mg.200g-1 rat's BW and red dragon fruit juice intervention dose of 6 gr.200g-1 rat's BW, 12 gr.200g-1 rat's BW and 18 gr.200g-1 rat's BW. Uric acid levels, XO activity, and NO levels were measured using FS TBHBA method, Xanthine Oxidase Chekine^{tm} Assay Kit, and Nitric Oxide (NO) Colorimetric Assay Kit. The difference in increased UA levels and the smallest XO activity indicated by the K2 group ($p < 0.05$), the smallest degree of decreasing the small number is shown by the K5 group ($p < 0.05$) compared to the K0 and K1 groups ($p < 0.05$). The K5 group has the most effective dose in preventing hyperuricemia and maintaining NO levels 140 mg.200g-1 rat's body weight.

Kata kunci:

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NO

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A B S T R A K

Hiperurisemia, suatu kondisi di mana kadar serum asam urat darah di atas normal, tidak hanya menjadi faktor resiko arthritis gout, namun juga faktor resiko penyakit kardiovaskuler. Buah Naga Merah / BNM (Hylocereus polyrhyzus) kaya akan flavonoid yang berpotensi sebagai antihiperurisemia. Penelitian ini bertujuan untuk membuktikan pengaruh pemberian jus BNM (Hylocereus polyrhizus) pada tikus hiperurisemia, dilihat dari aktivitas enzim xanthine oxidase dan kadar nitric oxide (NO). Metode yang digunakan ialah a true-experimental randomized dengan pre-post control group design. Tikus diinduksi dengan kaldu blok dan potasium oksonat. Sampel pada penelitian ini berjumlah tiga puluh ekor tikus Wistar (Rattus norvegicus) yang dibagi menjadi 6 kelompok perlakuan, yaitu kontrol negatif (K_0), kontrol positif (K_1), dan kelompok intervensi (K_2, K_3, K_4, K_5). Intervensi diberikan selama 28 hari dengan allopurinol 1,8 mg/200 g BB/hari dan intervensi jus BNM (Hylocereus polyrhizus) dosis 6 gr/200 gr BB, 12 gr/200 gr BB dan 18 gr/200 gr BB. Kadar asam urat serum, aktifitas

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XO, dan kadar NO diukur dengan metode FS TBHBA, CheKine™ Xanthine Oxidase Assay Kit, dan Nitric Oxide (NO) Colorimetric Assay Kit. Peningkatan kadar AU dan aktifitas XO paling kecil ditunjukkan oleh kelompok K_2 ($p<0,05$), selisih penurunan kadar NO paling kecil ditunjukkan oleh kelompok K_5 ($p<0,05$) dibandingkan kelompok K_0 dan K_1 ($p<0,05$). Kelompok K_5 memiliki dosis yang paling efektif dalam mencegah terjadinya hiperurisemia dan menghambat penurunan kadar NO.

INTRODUCTION

Hyperuricemia is a metabolic disease with increased serum uric acid levels as a result of increased uric acid formation or reduced uric acid excretion by the kidneys, or both ratiwi (Maruhashi T, 2013) (Thottam et al., 2017). Hyperuricemia is not only a risk factor for gout, but also a major determinant of hypertension, diabetes mellitus, chronic kidney disease, and cardiovascular disease (Kim et al., 2018) (Pramanik et al., 2015). Several studies have shown a significant role of hyperuricemia in the occurrence of vascular endothelial dysfunction which is the main mechanism in triggering atherosclerosis. Uric acid has also been shown to stimulate the synthesis of monocyte chemoattractant protein-1 (MCP-1) in vascular smooth muscle cells which is known to play an important role in stimulating macrophage infiltration in atherosclerosis (Gliozzi et al., 2016).

Red dragon fruit *(Hylocereus polyrhizus)* is a plant source of antioxidants. Red dragon contains bioactive compounds in the form of phenolic compounds such as flavonoids (anthocyanins, betacyanins, betaxanthine) vitamin C, and fiber that can reduce the risk of cancer, heart disease and diseases with oxidative stress (Gede et al., 2019) (Sim Choo & Khing Yong, 2011)(Senadheera & Abeysinghe, 2015)(Nourah Faadlilah & Martha Ardiaria, 2016). Flavonoid compounds have been known to have the ability to inhibit the activity of the xanthine oxidase enzyme (Amir & Purukan, 2018). Flavonoids are also known to stimulate the production of nitric oxide which plays a role in the process of vasodilation of blood vessels (Gliozzi et al., 2016).

Flavonoid compounds can act as xanthine oxidase (XO) inhibitors because they have a similar structure to xanthine. The similarity of flavonoids to xanthine is due to the presence of two aromatic rings which have a hydroxyl group as an electron acceptor of xanthine oxidase (XO) (Setyawan, 2015). This study aims to determine the effect of giving red dragon fruit juice *(Hylocereus polyrhizus)* on hyperuricemic conditions, seen from the activity of the xanthine oxidase enzyme and blood nitric oxide levels in hyperuricemic rats (Sim Choo & Khing Yong, 2011).

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METHODS

This study was a true exsperimental reaserch design using a randomized pre-post-test control group design. The research was conducted at the Inter-University Center for Studies and Nutrition Center Laboratory (PSPG PAU) Universitas Gadjah Mada Yogyakarta, from August 2020 to October 2020. The research began with harvesting red dragon fruit, followed by nutritional analysis and intervention in experimental animals. at PSPG Animal Laboratory PAU UGM Yogyakarta for 28 days with an acclimatization process for blood collection and analysis. Research on experimental animals has been approved by The Ethical Committee of Medical Research of Faculty of Medicine, Universitas Diponegoro, Semarang (No. No. 24/EC/H/FK-UNDIP/IV/2020.), Indonesia.

The Processing of Red Dragon Fruit Juice *(Hylocereus polyrhizus)*

The red dragon fruit sample used was the fresh red dragon fruit type Sabila Red which had been patented by the Yogyakarta Agriculture Service. from Sabila Farm, Kaliurang Km.18.5, Pakem, Yogyakarta, with a harvest age of 33 days after the flowers appear. The process of making red dragon fruit juice begins with peeling the skin, cutting the fruit flesh into small pieces and weighing it with a digital scale as needed. The dragon fruit was then mashed with a blender and placed in an erlenmeyer, then the dragon fruit juice was homogenized using a homogenizer for 30 seconds. Dragon fruit juice will be purplish red in color and have a thick texture.

Red Dragon Fruit Juice *(Hylocereus polyrhizus)* Nutritional Analysis

Analysis of the content of red dragon fruit juice *(Hylocereus polyrhizus)* was carried out using the proximate test, while the components measured were ash, water, carbohydrates, protein and fat content measured per 100 ml of juice. In addition, the analysis of antioxidant content was also carried out using the DPPH method. Identification of flavonoid levels was also carried out in this study. Analysis of flavonoid levels was carried out at the Chemical Laboratory of the Center for Food and Nutrition Studies (PSPG) of PAU Gadjah Mada University using the spectrophotometric method.

Exsperimental Animals

Wistar rats *(Rattus norvegicus)* were obtained from Animal Laboratory of Universitas Gadjah Mada, Yogyakarta, Indonesia. The acclimatization process was carried out for 7 days before the intervention to adjust the mice to the new environment and reduce stress on the mice. The rats (except K0) induced with Maggi brand block broth (PT Nestle, Indonesia) at an amount of 140 mg.200g-1 rat′s body weight and potassium oxonate (PO; Sigma Aldrich, USA) at a dose of 50 mg.200g-1 body weight. Thirty rats were divided into six groups, healthy control (K0) which received no induction and no treatment, hyperuricemic control group (K1) the hyperuricemia group with no treatment, (K2) the hyperuricemia group which was given allopurinol at the dose of 1.8 mg.200g-1 body weight, (K3) the hyperuricemia

group with red dragon fruit juice intervention dose of 6 gr.200g-1 body weight, (K4) the hyperuricemia group with red dragon fruit juice intervention dose of 12 gr.200g-1 body weight, and (K5) the hyperuricemia group with red dragon fruit juice intervention dose of 18 gr.200g-1 body weight. The rats were given oral intervention red dragon fruit juice for 28 days.

Laboratory Methods

Monitoring body weight of rats was carried out once every 7 days. Blood samples were examined 3 times to monitor the uric acid levels. The activity of the xanthine oxidase enzyme and the levels of nitric oxide in the blood of rats were carried out twice, before and after treatment. Uric acid levels, XO activity, and NO levels were analyzed using the FS TBHBA method, Chromatography, CheKine™ Xanthine Oxidase Assay Kit and Nitric Oxide (NO) Colorimetric Assay Kit. Rat blood samples were collected from the sinus orbital (±2mL) and centrifuged at 1,000 rpm for 15 minutes at 2 – 8 °C, plasma was collected and stored at -80 °C for later analysis. The analytical procedures were done according to the instruction of the kits. Thirty samples were analyzed, and each sample was measured twice (duplicate). Each treatment group consisted of five rats.

Statistical Analysis

The data obtained were analyzed statistically using the SPSS version 23.0 program. The data in this study are normally distributed, so that it is expressed as mean ± SD. Differences before and after the intervention were tested using Paired T-test, while the different effects of the five treatments were analyzed using One Way Anova followed by Post Hoc Bonferroni for data with normal distribution.

RESULT AND DISCUSSION

In this study, proximate analysis, antioxidant activity and flavonoid levels of red dragon fruit juice were measured before the start of the experiment at the Chemical Laboratory of the Center for Food and Nutrition Studies (PSPG) of PAU University of Gadjah Mada. Based on the results of the proximate test, 100 ml of red dragon fruit juice contains 87.86% water, 0.49% ash, 0.79% fat, 1.74% protein and 9.12% carbohydrates. Tabel 1. show the results obtained, the percent inhibition of red dragon fruit juice was 44.25%. Previous research by Pratama.R, 2017 obtained an IC50 value of antioxidant activity of 128.3764 g/ml and is included in the category of moderate antioxidant activity (Pratama R, 2017) (Han et al., 2012). This is because dragon fruit juice is a liquid that still contains the entire composition of the fruit where in a dragon fruit juice it still contains water, carbohydrates, protein, fat and other nutrients that may have anti-nutritional properties or can be oxidized more easily (Nancy Tombokan, 2017) (Akar et al., 2017). Identification of flavonoid was using the spectrophotometric method. Based on the results of the identification of flavonoid levels, in 100 grams of juice seen on Tabel 2. contains 34.35 mg of flavonoids. Similar results were also found in the study of Pratiwi.N.F et al in 2019 with the results of total flavonoid levels in red dragon fruit *(Hylocereus polyrhizus)* 36.25 mg QE (Pratiwi N.F et al., 2019) (Luo et al., 2014).

Tabel 1.
Antioxidant Activity (percent inhibition)

Methods	Materials	(%)Inhibition
DPPH	Red dragon fruit juice (*Hylocereus polyrhizus*)	44,25

Tabel 2.
Flavonoids Levels in 100 Grams of Red Dragon Fruit Juice

Methods	Materials	Result
Spectrophotometry	Red dragon fruit juice (*Hylocereus polyrhizus*)	34,35 Mg/100g

Weighing the rats aimed to monitor weight gain and determine the initial dose of red dragon fruit and allopurinol. The increase of body weight measurement showed in all treatment groups. The increase in body weight was caused by ad libitum feeding. Giving block broth also played a role in increasing the body weight of the mice. This study showed that hyperuricemia conditioning caused an increase in body weight of rats in all treatment groups (Shirasawa et al., 2020). The highest increase in body weight occurred in rats in the K1 (data not shown). The increase in body weight in all treatment groups was also related to growth factors with increasing age of the rats. In addition, this study also proves that the intervention of red dragon fruit juice *(Hylocereus polyrhizus)* can suppress the weight gain of mice that are too significant (Palak A.S & Gaurang B Shah., 2015).

Serum uric acid level measurement showed on Tabel 3. The significant increase in K1 (control) with total increase in uric acid levels before and after treatment was 8.452 mg/dL or 86.45% of uric acid levels increases. The smallest increase in uric acid levels occurred in the K2 (allopurinol) with an increase from the previous 8.58% uric acid level. The increase in uric acid levels also occurred in the three treatment groups with red dragon fruit juice, but the increase in uric acid levels that occurred in the three treatment doses was still in the normal category (Ariyanti et al., 2007)(Rahmawati & Kusumastuti, 2015). The K5 group showed the most effective inhibition of increasing blood uric acid levels, with uric acid levels after treatment of 1.898 mg/dL. Flavonoids are believed to play a significant role in inhibiting the increase in uric acid levels (Wang et al., 2016). Flavonoids can inhibit the work of the enzyme xanthine oxidase which is a catalyst for the formation of uric acid in the body. A previous study reported a decrease in uric acid levels by giving red onion juice at a dose of 7.0 mg/kg-1/day-1 able to reduce uric acid levels in hyperuricemic rats induced by potassium oxonate. This is because onion is one of the foods that are rich in flavonoids.

XO activity was measured twice, before and after the intervention. The average activity of XO before treatment was 35.65 mU/ml. Based on the results of this study, it was known that there was a change in XO enzyme activity before and after administration of red dragon fruit juice in rats with hyperuricemia conditions. An increase occurred in all treatment groups. A significant increase was seen in the K1 which was the positive control group. The XO activity increase also seen in K0, K2 and K5. The presence of high flavonoid content in red dragon fruit juice is believed to contribute to inhibiting XO activity in hyperuricemic rats. Previous studies have shown that the role of flavonoids is similar to the mechanism of action of allopurinol (Siu et al., 2006) . When low molecular weight phenolic compounds enter the pocket of the enzyme xanthine oxidase, these phenolics can act as a "plug" causing inhibition of the next

step, namely the formation of uric acid (Givertz et al., 2015). This proves that the administration of red dragon fruit juice can inhibit the increase in XO activity associated with an increase in blood uric acid levels whose mechanism of action is the same as allopurinol (Alghamdi et al., 2020).

Tabel 3.
Statistic analysis of Uric Acid Level

Uric Acid Level (mg/dL)	Groups					
	K0	K1	K2	K3	K4	K5
Pre	1,618 ± 0,135	1,324 ± 0,124[a]	1,512 ± 0,323	1,684 ± 0,219 [b]	1,694 ± 0,104[b]	1,554 ± 0,166
Post	1,830 ± 0,115	9,776 ± 0,098[a]	1,654 ± 0,328 [b]	3,908 ± 0,141[abc]	2,928 ± 0,313[abcd]	1,898 ± 0,033 [bde]
Δ	0,212 ± 0,327	8,452 ± 0,188 [a]	0,142 ± 0,022 [b]	2,224 ± 0,312 [abc]	1,234 ± 0,407 [abcd]	0,344 ± 0,150 [bde]
p	0,001*	0,001*	0,001*	0,001*	0,002*	0,007*

Note: Six group of rats consister of K0: normal rats; K1: hyperuricemia rats; K2: the allopurinol at the dose of 1.8 mg.200g-1 body weight ; K3: the red dragon fruit juice intervention dose of 6 gr.200g-1 body weight ; K4: the red dragon fruit juice intervention dose of 12 gr.200g-1 body weight ; K5: the red dragon fruit juice intervention dose of 18 gr.200g-1 body weight; Uric acid level of rats = *(mean SD)*; n= 5 mice/group; *p=Test Paired T-Test*; p1= *One Way ANOVA test*; x=*Mann-Whitney test*.

Increased activity of the xanthine oxidase enzyme is associated with the incidence of hyperuricemia, the xanthine oxidase enzyme plays a role in catalyzing the hydroxylation of hypoxanthine to xanthine and xanthine to uric acid (Nagao et al., 1999). Figure 1. shows that three doses of red dragon fruit juice were said to be able to inhibit the increase in XO activity in hyperuricemic rats in a dose-dependent manner, where the most effective dose was seen in the K5 group which was the treatment group with the largest dose (18 g/200 g BW). The increase from the previous XO activity in the K5 group was 4.61 mU/ml or 4.61% of the XO activity before treatment.

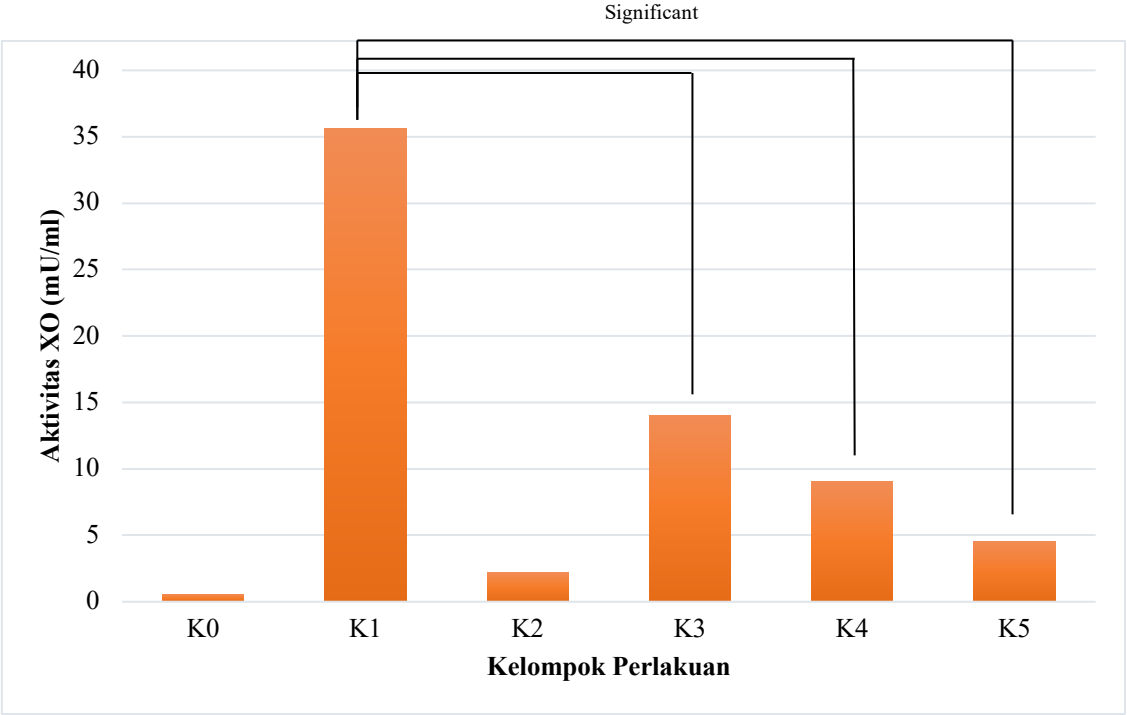

Figure 1.
Difference in Increase in XO Activity During Intervention of Red Dragon Fruit Juice *(Hylocereus polyrhizus)*

Figure 2. shows a significant reduction in NO levels in the hyperuricemic rat group before and after the intervention of red dragon fruit juice *(Hylocereus polyrhizus)* or allopurinol. The decrease in NO levels occurred in all treatment groups (K0, K1, K2, K3, K4 and K5) with p value = 0.001. A very significant reduction in NO was seen in the K1 group which was the positive control in this study. The results of the One Way ANOVA test also showed significant differences in NO levels after treatment. In the red dragon fruit juice treatment group (K3, K4, K5), the reduction in NO levels could be inhibited, and this inhibition was dose-dependent. The K5 group with a dose of 18 gr/200 gr BW red dragon fruit juice was the best intervention dose when compared to the other two intervention doses of red dragon fruit juice. Based on these results, it appears that the intervention of red dragon fruit juice *(Hylocereus polyrhizus)* has an effect on NO levels in hyperuricemic rats (Mahdi et al., 2019) (Kundi et al., 2018).

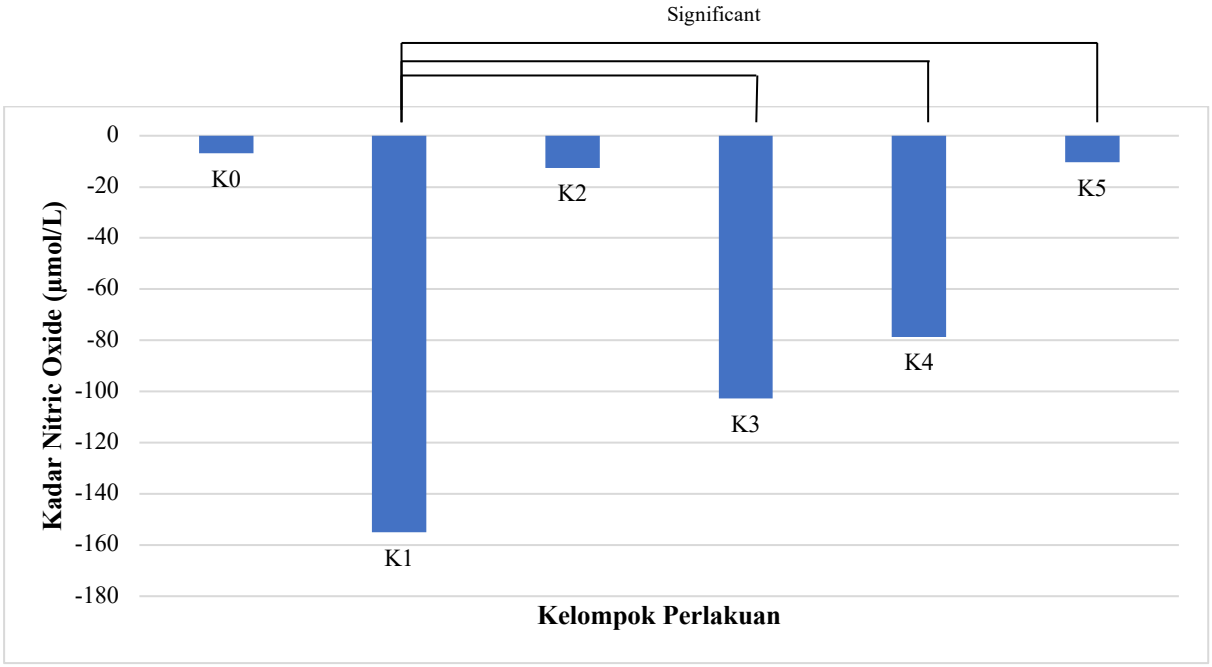

Figure 2.
Difference in Increase in XO Activity During Intervention of Red Dragon Fruit Juice *(Hylocereus polyrhizus)*

Nitric oxide levels were examined twice in this study, before and after the intervention of red dragon fruit juice and Allopurinol. NO levels are closely related to the condition of blood vessel walls, several studies have stated that NO plays a role in regulating blood vessel tone[107,108]. The highest reduction in NO levels was shown by the K1 (control). The average nitric oxide level before treatment was 235.83 mol/L and the average NO level after treatment was 17.77 mol/L. This proves that hyperuricemia is closely related to a decrease in blood NO levels, which is an indicator of poor blood vessel health (Hamid Musa et al., 2015). A decrease in blood NO levels also occurred in the treatment group with the administration of red dragon fruit (Hylocereus polyrhizus) juice. The best results were shown by K5 (treatment group) with the lowest reduction in NO levels compared to the other two doses, with a decrease in NO levels of 10.46 mol/L. The K5 was even able to inhibit the reduction of NO levels better than the treatment group with Allopurinol. This is supported by previous research which states that a diet high in flavonoids (quercetin & catechins) derived from grapes will induce an increase in NO. NO production and cyclic GMP content in the resting rat aorta will affect the endothelial state. The absence of increased expression of eNOS indicates that the mechanism of action of flavonoids is not a transcriptional mechanism. The antioxidant activity of flavonoids also has a protective function against atherosclerosis, by reducing the susceptibility of LDL to oxidation as well as being a vasodilator (Goicoechea et al., 2010)(Riegersperger et al., 2011).

CONCLUSIONS AND SUGGESTIONS

The effect of red dragon fruit juice *(Hylocereus polyrhizus)* is known to inhibit the increase in xanthine oxidase activity and prevent the reduction of nitric oxide levels in the blood of rats induced by hyperuricemia. Group K5 was the better and almost similar effective results of the group of rats treated with allopurinol. The increase in uric acid levels is proportional to the decrease in NO levels, consumption of red dragon fruit juice (Hylocereus polyrhyzus) can reduce the detrimental effect of hyperuricemia in terms of blood NO levels.

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ETHICAL CONSIDERATIONS

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Conflict of Interest Statement

There are no conflicts of interest.

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