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Anti-hyperurisemic Activity of Combination of Beetroot Powder (*Beta vulgaris L.*) And Allopurinol in Potassium Oxonate-Induced White Rats

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ABSTRACT

Introduction: Hyperuricemia is an abnormally high quantity of uric acid in the blood. Allopurinol is a type of xanthine oxidase inhibitor commonly used to lower uric acid levels in the general population. However, large doses of allopurinol can produce harmful effects, one of which being hepatotoxicity. The antioxidant activity of beetroot powder is high, and it has an antihyperuricemic effect. Giving beetroot powder and allopurinol together is intended to minimize allopurinol's adverse effects and give a positive increase in lowering uric acid levels. This study aims to evaluate the anti hyperuricemia effect of beetroot powder (*Beta vulgaris L.*) and allopurinol combination in white rats (*Rattus novergicus* strain Sprague Dawley) induced by potassium oxonate.

Methods: This an experimental study with a randomized pre and post-test control group design. In this experiment, twenty rats were placed into four treatment groups; KP = Positive Control (hyperuricemic rats) + standard feed and drink; G1 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day); G2 = Hyperuricemic rats + beet powder 1.56 g/Kg BW/day; G3 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day and beetroot powder 1,56 g/Kg BW/day. On day 0 and day 28, the amounts of uric acid were measured. Data obtained were analyzed using SPSS version 23 for windows.

Results: The mean pre-post changes in uric acid levels in each group were KP = 8.97 ± 0.48 mg/dl, G1 = 2.06 ± 0.15 mg/dl, G2 = 2.24 ± 0.10 mg/dl, and G3 = 2.11 ± 0.86 mg/dl. The mean pre-post changes in MDA levels in each group were KP = 8.14 ± 0.39 nmol/mL, G1 = 2.01 ± 0.38 nmol/mL, G2 = 3.13 ± 0.30 nmol/mL, and G3 = 2.35 ± 0.19 nmol/mL.

Conclusion: Beetroot powder and allopurinol combination given for 28 days significantly reduced uric acid and MDA levels in potassium oxonate-induced white rats.

Keywords: beetroot powder, allopurinol, hyperuricemia
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INTRODUCTION

In Indonesia, hyperuricemia is estimated to affect 1.7 percent of the population. This number can increase with age.[1] According to Riskesdas (2018), Riskesdas common illness affects 45 percent of people aged 55 to 64, 51.9 percent of people aged 65 to 74, and 54.8 percent of people aged 75 and above.[2] The prevalence of common illness is 7.3 percent based on health worker diagnoses and 24.7 percent based on symptoms. Hyperuricemia is common in men, with a prevalence of 17.7 percent and 5.2 percent in women. Men lack estrogen, the hormone which aids in the excretion of excess uric acid through the urine. Women are more susceptible to hyperuricemia as they age because the menopausal phase decreases the production of the hormone estrogen.[3]

In humans, uric acid is the result of purine metabolism. Uric acid is made by the enzyme Xanthine Oxidase (XO), which catalyzes the last two steps of the uric acid conversion, namely the conversion of hypoxanthine to xanthine and the formation of uric acid.[4] Elevated uric acid can induce oxidative stress and ROS (Reactive Oxygen Species) production in vascular endothelial cells. Massive ROS can upregulate IL-6, and TNF-α expression.[5] Uric acid is positively correlated with Malondialdehyde.[6] Malondialdehyde (MDA) is a lipid peroxidation product that may be easily identified in blood or plasma and is used as an oxidative stress indicator.[7,8] According to a study by Zhou et al. (2018), people with hyperuricemia have greater MDA and lower SOD levels than healthy people.[9]

Allopurinol is a XO inhibitor frequently used by the public to lower uric acid levels. Treatment failure is reported in 25-50 percent of patients with hyperuricemia due to a suboptimal response to the drug at the recommended dose, failure to tolerate side effects or contraindications.[10] The most common side effects of allopurinol are gastrointestinal intolerance and skin rashes.[11] Another treatment and therapy

option for hyperuricemia is dietary management, which includes consuming antioxidant-rich foods. Beetroots contain betacyanin pigments, which give them a purplish red color. Betacyanin is a betalain derivative that belongs to the flavonoid family and has been shown to have potent antioxidant properties. Several studies have reported that antioxidants have an antihyperuricemic effect.[1,12,13]

Based on the previous explanation, the purpose of this study is to evaluate the anti-hyperuricemic potential of beetroot powder (*Beta vulgaris L.*) and allopurinol combination in white rats (*Rattus novergicus* strain Sprague Dawley) induced by potassium oxonate. The animal model used in this is rats because the genetic, biological and behavioral characteristics of rats are similar to those of humans.

METHOD

This research was experimental research with pre and post-test design using control group design. The rats were kept in the House of Experimental Rats CFNS Central Laboratory of Food and Nutrition, PAU, Universitas Gajah Mada, Yogyakarta. The animal model used in this experiment was male rats (*Rattus novergicus*) strain Sprague-Dawley. Male rats were chosen because they lack the estrogen hormone. The estrogen can aid in the excretion of uric acid through the urine, resulting in normal uric acid levels.[14]

This research involved several stages, namely the production of beetroot powder, the screening for antioxidant content, the creation of hyperuricemia rat models, the intervention, and the measurement of uric acid and MDA levels before and after treatment. The beetroots used were six weeks old when harvested. The production of beet powder started with sorting, trimming, washing, size reduction, drying, milling, and 80 mesh sifting.

The hyperuricemia rat model was created by injecting 250 mg/kg BW/day potassium oxonate intraperitoneally for 14 days.[15] The Federer formula was used to determine the number of minimal samples needed in this research. Twenty hyperuricemic rats were randomized and then divided into four groups, with five rats in each group. KP = Positive Control (hyperuricemic rats) + standard feed and drink; G1 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day); G2 = Hyperuricemic rats + beet powder 1.56 g/Kg BW/day; G3 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day and beetroot powder 1,56 g/Kg BW/day. Allopurinol, commonly used by the public, is a tablet with a dose of 100 mg.[16] The dose conversion from a human (70 kg) to a rat (200 g) was 0,018. The dose of allopurinol given to rats was: 100 mg x 0,018 = 1,8 mg/kg body weight /day. The administration of allopurinol and beetroot powder was intervened through a gastric probe once a day. The treatment was given for 28 days every 09.00 to 10.00 a.m.

The uric acid levels were examined using uric acid reagent FS TBHBA. The TBARS (Thiobarbituric acid reactive substance) was used to measure MDA levels. Examination of uric acid levels and MDA were carried out three times (before induction, after induction/day 0 of intervention and day 28 following intervention). Data collected then analyzed using SPSS ver.23 for windows.

The research was conducted at UGM's Central Laboratory of Food and Nutrition Studies, with certification number: ISO/IEC 17025:2000. Magnesium and calcium levels were tested at the Analytical Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada; testing for total phenolic, antioxidant activity, and vitamin C was carried out at the Food Technology and Agricultural Products Laboratory, Faculty of Food Technology, Universitas Gadjah Mada. This research has obtained permission from the Research Ethics Board, Faculty of Medicine, Universitas Sebelas Maret, with number: 468/UN27.06/KEPK/EC/2019.

RESULTS

Screening for Nutrient Content of Beetroot Powder

Beetroot powder was tested for antioxidant and mineral content to obtain supporting data. The results for antioxidant and mineral content are listed in **Table 1**.

Uric Acid Levels in Hyperuricemia Rats Model

Before and after induction, the measurement of uric acid levels aims to determine the effect of potassium oxonate on changes in uric acid levels in rats.

The mean uric acid levels increased significantly ($p < 0.05$) before and after

Table 1. Antioxidant and mineral content of beetroot powder

Antioxidant and mineral content	Result
Ca	4149,070 ppm
Mg	3131,938 ppm
Total phenolic	34,02 mg GAE/gr
Antioxidant activity DPPH	67,89%
Vitamin C	925,68 mg/100 g

Source : Primary Data (2020)

Table 2. Uric acid levels means before and after induction

Group	Before induction (mg/dl; mean ± SD)	After induction (mg/dl; mean ± SD)	Δ Levels of Uric Acid (mg/dl; mean ± SD)	P[a]
KP	1,37 ± 0,08	8,97 ± 0,48	7,60 ± 0,47	0,043*
G1	1,48 ± 0,06	8,79 ± 0,54	7,30 ± 0,54	0,042*
G2	1,44 ± 0,07	8,60 ± 0,55	7,15 ± 0,52	0,043*
G3	1,43 ± 0,11	8,84 ± 0,72	7,40 ± 0,77	0,043*
P[b]	0,258	0,868	0,702	

Source : Primary Data (2020)

*There is a significant difference with p<0.05 (*Wilxocon*[a] test and *Kruskal Wallis*[b] test)

Note : KP = Positive Control (hyperuricemic rats) + standard feed and drink; G1 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day); G2 = Hyperuricemic rats + beet powder 1.56 g/Kg BW/day; G3 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day and beetroot powder 1,56 g/Kg BW/day

Table 3. The average uric acid level before and after 28 days of treatment

Group	Duration			P[a]
	Day-0 (mg/dl; mean ± SD)	Day-28 (mg/dl; mean ± SD)	Δ Levels of Uric Acid (mg/dl; mean ± SD)	
KP	8.97 ± 0.48	9.38 ± 0.19	0.41 ± 0.38	0.061
G1	8.79 ± 0.54	2.06 ± 0.15	-6.72 ± 0.59	0.043*
G2	8.60 ± 0.55	2.24 ± 0.10	-6.35 ± 0.61	0.043*
G3	8.84 ± 0.72	2.11 ± 0.86	-6.72 ± 0.75	0.043*
P[b]	0.086	0.003*	0.009*	

Source: Primary Data (2020)

* There is a significant difference as p<0.05 (*Wilxocon*[a] test and *Kruskal Wallis*[b] test)

Note : KP = Positive Control (hyperuricemic rats) + standard feed and drink; G1 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day); G2 = Hyperuricemic rats + beet powder 1.56 g/Kg BW/day; G3 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day and beetroot powder 1,56 g/Kg BW/day

Table 4. Comparison of average uric acid levels on 28th day of treatment

Groups (I and II)	Δ Levels of Uric Acid (nmol/mL; mean ± SD)		p
	I	II	
KP and G1	9,38 ± 0,19	2,06 ± 0,15	0,009*
KP and G2	9,38 ± 0,19	2,24 ± 0,10	0,009*
KP and G3	9,38 ± 0,19	2,11 ± 0,86	0,009*
G1 and G2	2,06 ± 0,15	2,24 ± 0,10	0,046*
G1 and G3	2,06 ± 0,15	2,11 ± 0,86	0,917
G2 and G3	2,24 ± 0,10	2,11 ± 0,86	0,047*

* There is a significant difference as p<0.05 (*Mann Whitney Test*)

Table 5. The average MDA level before and after treatment

Group	Duration			P[a]
	Day-0 (Mean ± SD) (nmol/mL)	Day-28 (Mean ± SD) (nmol/mL)	Δ Levels of MDA (nmol/mL)	
KP	7.55 ± 0.32	8.14 ± 0.39	0.58 ± 0.31	0.013*
G1	7.57 ± 0.27	2.01 ± 0.38	-5.55 ± 0.30	0.001*
G2	7.48 ± 0.34	3.13 ± 0.30	-4.35 ± 0.51	0.001*
G3	7.82 ± 0.37	2.35 ± 0.19	-5.47 ± 0.39	0.001*
P[b]	0.425	0.001*	0.001*	

Source: Primary Data (2020)

* There is a significant difference as p<0,05 (*Paired T-test*[a] and *One Way Anova*[b] *test*)

Note : KP = Positive Control (hyperuricemic rats) + standard feed and drink; G1 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day); G2 = Hyperuricemic rats + beet powder 1.56 g/Kg BW/day; G3 = hyperuricemic rats + allopurinol 1,8 mg/Kg BW/day and beetroot powder 1,56 g/Kg BW/day

Table 6. Differences in MDA level changes in 28 days of treatment

Group (I and II)	Δ Levels of MDA (nmol/mL; mean ± SD)		p
	I	II	
KP and G1	0,58±0,31	-5,55±0,30	0,001*
KP and G2	0,58±0,31	-4,35±0,51	0,001*
KP and G3	0,58±0,31	-5,47±0,39	0,001*
G1 and G2	-5,55±0,30	-4,35±0,51	0,041*
G1 and G3	-5,55±0,30	-5,47±0,39	0,067
G2 and G3	-4,35±0,51	-5,47±0,39	0,042*

Source : Primary Data (2020)

* There is a significant difference as p<0,05 (*Post Hoc Test*)

calcium oxonate induction, as shown in Table 2. The KP group had the highest mean of the uric acid level after induction (8.97 ± 0.48 mg/dl), while the G2 group had the lowest mean of the uric acid level after induction (8.60 ± 0.55 mg/dl). Uric acid levels were substantially different before and after calcium oxonate induction ($p < 0.05$).

Table 3 demonstrates how uric acid levels changed after 28 days of intervention. The Wilcoxon and Kruskal-Wallis tests were employed to examine the data. From table 3, after 28 days of intervention, there was a substantial increase in the average uric acid level in KP with p-value = 0.043 ($p < 0.05$) and a significant decrease in the uric acid level in G1, G2, and G3 with a p-value = 0.043 ($p < 0.05$).

Table 3 shows that on day 28, the average decrease in uric acid levels in the group varied from -6,35 ± 0,61mg/dl to -6,72 ± 0,75 mg/dl. The KP group is the only group which uric acid level has increased. The KP group had the highest uric acid levels (9.38 ± 0.19 mg/dl), and the G1 group has the lowest (2.06 ± 0.15 mg/dl). The G1 (-6.72 ± 0.59 mg/dl) and G3 (-6.72 ± 0.75 mg/dl) had almost the same decrease in the mean uric acid levels. Table 3 reveals that 28 days of beetroot powder and allopurinol treatment can bring uric acid levels back to normal (1.18-3.56 mg/dl).

The difference in uric acid levels between groups was assessed to see which groups affected lowering uric acid levels on day 28 and whether there were differences in uric acid levels between groups. Table 4 shows the differences in uric acid levels between treatment groups on day 28th.

According to Table 4, uric acid levels in groups G1 and G2 (p = 0,046); G2 and G3 (p = 0,047) declined more rapidly on day 28 than in the other groups (p = 0,009). The decrease in uric acid levels in groups G1 and G3 was nearly identical, with a p-value of 0.917 ($p < 0.05$).

MDA Levels in Model Hyperuricemia Rats

Table 5 shows the change in MDA data after 28 days of intervention. The data were tested using paired t-test and One-Way Anova. According to Table 5 there was a significant increase in the mean MDA in

KP with p-value = 0.13 ($p < 0.05$) and a significant decrease in the mean MDA in G1, G2, and G3 with p-value = 0.001 ($p < 0.05$) after 28 days of intervention.

Table 5 shows that on day 28th, the average decrease in MDA levels in the group ranged from -4.35 ± 0.51 nmol/mL to -5.55 ± 0.30 nmol/mL, the KP group increased by 0.458 ± 0.31 nmol/mL. The highest MDA level was seen in the KP group (8.14 ± 0.39 nmol/mL) and the lowest in the G1 group (2.01 ± 0.38 nmol/mL).

Differences in the decrease in MDA levels between groups were analyzed to determine which groups affected reducing MDA levels on day 28 and whether there were differences between groups in decreasing MDA levels. **Table 6** shows the differences in changes in MDA levels between treatment groups. According to table 6, uric acid levels in groups G1 and G3 decreased at nearly the same rate and were higher than the other groups ($p < 0.05$).

DISCUSSION

High uric acid levels can trigger the activity of the enzyme Xanthine Oxidase (XO). Excessive XO activity increases Reactive Oxygen Species (ROS) formation, causing an increase in the lipid peroxidase process. Malondialdehyde (MDA) is formed due to lipid peroxidation, which is easily detected in blood or plasma and is used to measure oxidative stress.[17,18]

Potassium oxonate is a reagent that functions as a urate oxidase inhibitor which gives a hyperuricemic effect. The mechanism of potassium oxonate in increasing uric acid levels is by preventing uric acid from becoming allantoin.[19] Potassium oxonate injection in rats caused a decrease in total serum antioxidant capacity and an increase in serum MDA levels. We also found that induction of hyperuricemia using calcium oxonate shows a significant increase ($p < 0.05$) in the mean uric acid levels after induction, and it is known that all groups have reached a state of hyperuricemia since uric acid levels were above average level (> 3,56 mg/dl). Therefore, the hyperuricemia rat model can be used to determine and evaluate the effect of giving beetroot powder.

We found that the positive control group (KP) with no treatment of allopurinol nor beetroot powder shows an increase in uric acid levels; meanwhile, the other treatment groups show a significant decrease in the uric acid levels. This can be caused by antihyperuricemia effect of the allopurinol and the beetroot powder. The antioxidant content found in beetroot powder is known to have a total phenolic content of 34,02 mg GAE/gr, and antioxidant activity is 67,89 percent. Beetroots contain betacyanin pigments that form a purplish red color. Betacyanin is a betalain derivative that belongs to the flavonoid family and has potent antioxidant properties.[20,21] It is in line with Asra et al., which reported that the percentage of betacyanin in beetroot was 98.6 percent, with an IC50 value of 21.8, indicating that it has a potent antioxidant activity ($IC_{50}<50$).[22] Several *in-vivo* and *in-vitro* studies have shown that antioxidants found in many plants, such as flavonoids and phenolics, have a genuine influence on uric acid problems by blocking the XO enzyme, boosting renal uric acid secretion, and reducing uric acid reabsorption.[1] Polyphenol and flavonoids, which have a similar structure to xanthine, act as XO enzyme inhibitors. Polyphenols and flavonoids function as substrates of XO enzymes. Polyphenols and flavonoids will bind electrons from the XO enzyme, which should oxidize xanthine to uric acid. This competition will decrease uric acid production because XO enzymes tend to oxidize polyphenols and flavonoids rather than xanthine. The interaction of XO enzymes, polyphenols, and flavonoids causes an increase in the concentration of non-oxidized xanthine in the serum, followed by the excretion of xanthine, which is easily soluble in urine, resulting in a decrease in serum uric acid levels.[23] Vitamin C content in beetroot powder is 925,68 mg/100 g. Vitamin C also has uricosuric properties, it can inhibits the uric acid reabsorption in the kidney tubules so that the speed at which the kidneys work to excrete uric acid through urine can increase.[12]

Beetroot contains Ca of 4.14 mg/g and Mg of 3.13 mg/g. Minerals like Ca and Mg can help reduce uric acid levels. According to Anggraini et al., dragon fruit containing Ca and Mg can reduce uric acid levels.[13] This is because the amount of uric acid oxidized by the uricase enzyme has occurred due to the ionization of uric acid with minerals that form uric acid salt compounds that are soluble in water. Under normal pH, uric acid will be ionized into urate ions, with cations, urate ions will form urate salts. Urate salt is a complex molecule generated when uric acid reacts with Ca^{2+} and Mg^{2+}.

This research showed that the mean of MDA levels in all treatment groups decreased significantly within the duration of treatment, except for the KP group, which increased significantly after the 28th day of the intervention. In model rats with high uric acid levels, beetroot powder exerts an antihyperuricemic effect, resulting in decreased MDA levels. Beetroot powder has robust antioxidant activity and has been shown to reduce MDA levels in hyperuricemic rats, as seen by a decrease in MDA levels in rats intervened with beetroot powder. Antioxidant compounds in food can reduce oxidative stress. Oxidative stress can cause lipid peroxidation reactions, proteins including enzymes and DNA, this can cause oxidative damage. If this condition persists, there will be cell damage and death. With a decrease in oxidative stress, diseases associated with it, such as hyperuricemia, can be inhibited due to antioxidant and anti-inflammatory activity in repairing oxidative damage.[7] Similarly, Wruss et al. argued that beetroot has a red color due to a high concentration of betalains compounds in beets.[24] Betalains are commonly utilized as natural colors in the food industry. Due to betalains antioxidant and anti-inflammatory properties, they also said to offer health benefits. In addition, betalains also have lipid peroxidation inhibiting properties.

One of this study's limitations was that the other oxidant/antioxidant parameters, such as superoxide dismutase (SOD) and nitric oxide (NO), were not measured. The other oxidant/antioxidant parameters' measurements may help determine the other antioxidant process that could decrease uric acid's blood levels by giving beetroot powder.

CONCLUSION

Beetroot powder and allopurinol combination that was given for 28 days significantly reduced uric acid and MDA levels in potassium oxonate-induced white rats.

ETHICAL CONSIDERATION

This research has received Ethical Clearance from the Ethical Committee, Faculty of Medicine, Universitas Sebelas Maret (No.468/UN27,06/KEPK/EC/2019).

CONFLICT OF INTEREST

The author reports that no conflict of interest in this works.

FUNDING

None.

AUTHOR CONTRIBUTION

The first author Anggraini Wulandari conceptualizes and designs research, prepares draft manuscripts, observe experimental animals, collects and analyzes the data; Paramasari Dirgahayu leads the field data collection, reviews the data and interpretations, helps to compile and review the manuscript; Budianti Wiboworini reviews the data, analyzes the data and interpretation, helps to prepare and review the manuscript.

REFERENCES

1. Mehmood A, Zhao L, Wang C, Nadeem M, Raza A, Ali N, et al. management of hyperuricemia through dietary polyphenols as a natural medicament: A comprehensive review. Crit Rev Food Sci Nutr. 2019;59(9):1433–55.
2. Riskesdas. Laporan Nasional Riskesdas 2018. Badan Penelitian dan Pengembangan Kesehatan. Badan Penelitian dan Pengembangan Kesehatan Kementerian RI tahun 2018.; 2018. p. 198.
3. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of Hyperuricemia and The Relationship Between Serum Uric Acid and Metabolic Syndrome in the Asian Mongolian Area. J Atheroscler Thromb. 2014;21(4):355–65.
4. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric Acid, Hyperuricemia and Vascular Diseases. Front Biosci (Landmark Ed. 2012;17:656–69.
5. Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PIH. Molecular Mechanisms of ROS Production and Oxidative Stress in Diabetes. Biochem J. 2016;473(24):4527–50.
6. Haidari F, Keshavarz SA, Shahi MM, Mahboob SA, Rashidi MR. Effects Of Parsley (Petroselinum Crispum) And Its Flavonol Constituents, Kaempferol And Quercetin, On Serum Uric Acid Levels, Biomarkers Of Oxidative Stress and Liver Xanthine Oxidoreductase Aactivity Inoxonate-Induced Hyperuricemic Rats. Iran J Pharm Res. 2011;10(4):811–9.
7. Sarvaiya VN, Sadariya KA, Pancha PG, Thaker AM, Patel AC. Evaluation of Antigout Activity of Phyllanthus Emblica Fruit Extracts on Potassium Oxonate-Induced Gout Rat Model. Vet World. 2015;8:1230–6.
8. Li L, Teng M, Liu Y, Qu Y, Zhang Y, Lin F, et al. Anti-Gouty Arthritis and Antihyperuricemia Effects of Sunflower (Helianthus annuus) Head Extract in Gouty and Hyperuricemia Animal Models. Biomed Res Int. 2017;2017:1–9.
9. Zhou Y, Zhao M, Pu Z, Xu G, Li X. Relationship between oxidative stress and inflammation in hyperuricemia. Medicine (Baltimore). 2018;97(49):e13108.
10. Su Q, Su H, Nong Z, Li D, Wang L, Chu S, et al. Hypouricemic and Nephroprotective Effects of an Active Fraction from Polyrhachis Vicina Roger on Potassium Oxonate-Induced Hyperuricemia in Rats. Kidney Blood Press Res. 2018;43(1):220–33.
11. Alqahtani MJ, Alshamrani AM. Overview of Allopurinol Decisions in Primary Care: A Narrative Review. Egypt J Hosp Med. 2018;72(2):3909–13.
12. Juraschek SP, Miller ER, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: A meta-analysis of randomized controlled trials. Arthritis Care Res. 2012;63(9):1295–306.
13. Anggraini DI, Suprijono A, Wahyusetyaningrum SL. Mineral Dalam Buah Naga (Hylocereus Undatus (Haw.) Britt. & Rose) Sebagai Penurun Asam Urat. J Ilm Kesehat. 2013;5(1).
14. Suhendi A, Nurcahyanti, Muhtadi, Sutrisna EM. Aktivitas antihiperurisemia ekstrak air jinten hitam (Coleus ambonicus Lour) pada mencit jantan galur balb-c dan standardisasinya Antihyperurisemia activity of water extract of black seed (Coleus ambonicus Lour) in balb-c mice and its standardi-. Maj Farm Indones. 2011;22(2):77–84.
15. Aprillinda FW, Paramasari D, Brian W. The Effect of Red Guava Juice (Psidium guajava Linn.) in Decreasing Uric Acid and Creatinine Levels of White Mice (Mus musculus) with Hyperuricemia. Bali Med J. 2018;7(2):323–9.
16. Wells BG., DiPiro JT, Schwinghammer TL, DiPiro C V. Pharmacotherapy Handbook. New York: McGraw-Hill-Open Acces Journal; 2012.
17. Luo C, Lian X, Hong L, Zou J, Li Z, Zhu Y, et al. High Uric Acid Activates the ROS-AMPK Pathway, Impairs CD68 Expression and Inhibits OxLDL-Induced Foam-Cell Formation in a Human Monocytic Cell Line, THP-1. Cell Physiol Biochem. 2016;40(3–4):538–48.
18. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016;213:8–14.
19. Kensara OA. Protective effect of vitamin C supplementation on oxonate-induced hyperuricemia and renal injury in rats. Int J Nutr Metab. 2013;5(June):61–6.
20. Wong YM, Siow LF. Effects of Heat, Ph, Antioxidant, Agitation and light On Betacyanin Stability Using Red-Fleshed Dragon Fruit (Hylocereus polyrhizus) Juice and Concentrate as Models. J Food Sci Technol. 2015;52(5):3086–92.
21. Novatama SM, Kusumo E, Supartono. Identifikasi Betasianin dan Uji Antioksidan Ekstrak Buah Bit Merah. Indo J Chem Sci. 2016;5(3):217–20.
22. Asra R, Rusdi R, Nofrianti R. Physicochemical Study of Mangosteen (Garcinia mangostana L.) peel Extract as Coloring Agent in Tablet Formulation. J Pharm Sci. 2020;3(1):22–32.
23. Al-azzawie HF, Abd SA. Effects of Crude Flavonoids from Ginger (Zingiber officinale), on Serum Uric Acid Levels, Biomarkers of Oxidative Stress and Xanthine Oxidase Activity in Oxonate-Induced Hyperuricemic Rats. Int J Adv Res. 2015;2(6):55–61.
24. Wruss J, Waldenberger G, Huemer S, Uygun P, Lanzerstorfer P, Müller U, et al. Compositional Characteristics of Commercial Beetroot Products and Beetroot Juice Prepared from Seven Beetroot Varieties Grown in Upper Austria. J Food Compos Anal. 2015;42(3):46–55.