Jurnal Aisyah: Jurnal Ilmu Kesehatan

Volume 8, Issue 2, June 2023, p. 135–140
ISSN 2502-4825 (print), ISSN 2502-9495 (online)

Red Cabbage Juice Decreases Oxidative Stress in Hyperuricemia Model Rats

Muhammad Abdul Rauf[1*)], Budiyanti Wiboworini[2], Paramasari Dirgahayu[3]

[1] Postgraduate Program of Nutrition Science, Universitas Sebelas Maret
[2] Department of Nutrition, Faculty of Medicine, Universitas Sebelas Maret
[3] Department of Parasitology, Faculty of Medicine, Universitas Sebelas Maret

ARTICLE INFO

Article history:

Received 21 November 2022
Accepted 1 April 2023
Published 10 June 2023

Keyword:

Hyperuricemia
Oxidative Stress
Red Cabbage Juice
Uric Acid
MDA

ABSTRACT

Serum uric acid levels are recognized to be a substantial risk factor for developing oxidative stress-related illnesses. Red cabbage has the largest concentration of anthocyanins of any antioxidant, which contributes to oxidative stress. This study aimed to see how anthocyanins in red cabbage juice affected MDA levels in hyperuricemia model rats at different dosages and times of the intervention. A Randomized Complete Design was used to create a before and post-test group research design with 24 male Sprague-Dawley rats aged 10-12 weeks classified into four groups, the Control Group (KN) and the Treatment Group (P1-3). KN rats received standard feed, whereas P1-3 received a regular meal and dosages of red cabbage juice of 1.8, 3.6, and 7.2 ml/200g BW for 28 days. Uric acid levels are measured before and after induction, whereas MDA levels are measured before the installation, after induction (Day 0), on Day 14, and on Day 28. Data analysis was performed utilizing the One Way Anova test, Repeated Measured ANOVA, and a mixed design. Statistical testing revealed that differences in dosage and intervention time duration significantly lowered MDA levels in all treatment groups (p0.05). On day 28, the red cabbage juice intake of 7.2 ml/200grBB returned MDA levels to normal.

Kata kunci:

Hiperurisemia
Stress Oksidatif
Jus Kubis Merah
Asam Urat
MDA

**) corresponding author*

Muhammad Abdul Rauf, S.ST

Postgraduate Program of Nutrition Science, Universitas Sebelas Maret
Jl. Ir. Sutami No.36, Surakarta, Jawa Tengah Indonesia 57126

Email: rauf.muhammadabdul@gmail.com
DOI: 10.30604/jika.v8i2.1750

ABSTRAK

Peningkatan asam urat serum diketahui menjadi risiko utama terkait perkembangan penyakit akibat stres- oksidatif. Kubis merah mengandung antosianin paling tinggi diantara jenis antioksidan lain yang berperan terhadap keadaan oksidatif stress. Tujuan penelitian ini untuk mengetahui pengaruh antosianin dari jus kubis merah dengan variasi dosis dan lama waktu intervensi terhadap penurunan kadar MDA tikus model hiperurisemia. Penelitian Pre and post-test group esign dengan Rancangan Acak Lengkap menggunakan 24 tikus jantan *Sprague-Dawley* umur 10-12 minggu dibagi menjadi 4 kelompok yaitu Kelompok kontrol (KN) dan Kelompok Perlakuan (P1- 3). Tikus KN diberi pakan standart sedangkan P1-3 diberi pakan standart ditambah jus kubis merah dosis 1.8, 3.6, 7.2 ml/200g BB selama 28 hari. kadar asam urat dipantau sebelum dan setelah induksi, untuk kadar MDA dipantau sebelum Induksi, setelah induksi/Hari ke0, Hari ke 14 dan Hari Ke 28. Data dianalisi menggunakan uji One Way ANOVA, Repeated measured ANOVA dan mix design. Hasil uji statistik menjelaskan variasi dosis dan lama waktu intervensi terbukti nyata menurunkan kadar MDA pada semua kelompok perakuan ($p<0,05$). Kesimpulannya jus kubis merah dosis 7,2 ml/200grBB mampu menurunkan kadar MDA mencapai batas normal pada hari ke 28.

This open access article is under the CC–BY-SA license.

INTRODUCTION

Hyperuricemia is a non-communicable condition characterized by elevated serum uric acid levels in the blood (Aletaha et al., 2010) . According to the World Health Organization (WHO), the prevalence of hyperuricemia is increasing yearly, with an incidence rate of 1-4% of the general population. This rise is also seen in emerging nations like Indonesia (Kumar & Lenert, 2016). According to Basic Health Research statistics from 2018, the prevalence of hyperuricemia illness is 7.3% of the entire population of Indonesia. According to age characteristics, the most immense majority of hyperuricemia patients at the age of 75 years was 18.95%, with a greater prevalence for women (8.46%) than males (6.13%), and the majority continues to rise with age (Fitriyah et al., 2011).

Hyperuricemia is defined as serum uric acid levels that are higher than usual, with male limits of 7.0 mg/dL and female limits of 6.0 mg/dL, due to increased activity of the enzyme xanthine oxidase (XO), which results in the accumulation of monosodium urate (MSU) crystals in blood cells and the development of inflammatory reactions (Cha et al., 2019; Fitriyah et al., 2011). Long-term collection of MSU crystals can lead to forming free radicals via reactive oxygen species (ROS) (Eleftheriadis et al., 2017; Sharaf El Din et al., 2017). As a result of increased uric acid synthesis, it produces superoxide radicals (Fabbrini et al., 2014). Free radicals can destroy cell membranes, resulting in lipid peroxidation and oxidative stress in the body (Maiuolo et al., 2016). Malondialdehyde (MDA) is the end product of lipid peroxidation and is a sign of oxidative stress (Renaudin et al., 2020)

To minimize oxidative stress in the body, hyperuricemia situations necessitate using exogenous antioxidants. Theories discuss the effects of exogenous antioxidants found in food items that can replace electrons in unstable cells, preventing cell membrane breakdown (Ali et al., 2020; Deng et al., 2021; Forman & Zhang, 2021). Wulandari et al. (2021) found that providing red beet flour 3.12 g/kg BW/day rich in antioxidants may lower MDA levels to normal for 28 days in hyperuricemia model male rats.

Aside from red beet flour, red cabbage is a typical antioxidant-rich food. Red cabbage is a widely known agricultural product among the general people. Lukitasari et al. (2017) discovered that red cabbage has high antioxidant activity, with an IC50 of 725.65 0.09 ppm. The studies showed that vitamin C levels in red cabbage ranged from 41 to 146 mg/100g, total phenolics ranged from 31 to 337 mg/100g, and carotenoids from 0.37 to 5.42 mg/100g (Bahorun et al., 2004; Franke et al., 2004; Wu et al., 2004). In summary, red cabbage also has a high level of anthocyanin antioxidants. Anthocyanins are antioxidant chemicals produced from flavonoids that give purplish red hues and are the most abundant antioxidant in red cabbage (Ghareaghajlou et al., 2021; Podse ̨dek et al., 2006). Because anthocyanins are polar and would dissolve in polar solvents, producing them in juice form is preferable for use in our investigation (Alappat & Alappat, 2020).

To this certain extent, researchers have not observed the effect of red cabbage juice in suppressing oxidative stress by reducing Malondialdehyde levels in hyperuricemia model rats. This study aims to test the dose variation and time variation of red cabbage juice administration to reduce MDA levels in potassium oxonate-induced rats.

METHODS

Animal Model and Research Design

This was an experimental laboratory study on rats with a pre and post-test design with a control group. The experimental setup is entirely randomized. Male Sprague-Dawley (SD) white rats aged 10-12 weeks were used in the study and were obtained from the Center for Food and Nutrition Studies at Gadjah Mada University in Indonesia. Rats were placed in cages of iron blocks 80x23.5x19 cm in size, divided into six tiny chambers, each occupied by one rat, and adapted for seven days. Temperature control (27-29oC), 12 hours of bright and 12 hours of dark lights were used for rat upkeep.

Sample Size and Study Protocol

The sample of 24 SD male white rats was determined based on the sample calculation by the E-value formula with degrees of freedom in the "resource equation" statistic (Ab, 2017). Rats were randomly divided into four groups: the Negative Control group (KN) and the Treatment Group (P1-3). Each rat group was supplemented with standard confessed, and adequate Treatments groups were supplemented with 1.8, 3.6 and 7.2 ml/200g BW of red cabbage juice daily in the order of treatment groups. The procedure for producing red cabbage juice was published at the 4th International Conference on Social Determinants of Health, Uhamka, Indonesia.

Animal procedures and experimental protocols in this study have been approved by the ethics committee of the Faculty of Medicine, Sebelas Maret University protocol number 83/UNS27.06.11/KEP/EC/ 2022.

Doses of Red Cabbage Juice

The dosages are calculated using a human anthocyanin consumption of 12.5 mg (Sebastian et al., 2015). It was also adjusted with a rat-to-human conversion factor to the anthocyanin content of red cabbage juice (2.84 g/100gram) (0.018). Red cabbage juice dosages in the trial were 1.8, 3.6, and 7.2 ml/200g body weight. The intermediate dosage (3.6 ml/kg BW/day) had anthocyanin content equal to the daily need based on experimental animal conversion. The low and high dosages were calculated by halving or doubling the standard dose.

Treatments and Data Collection Procedures

To establish that rats were already in hyperuricemia, blood samples for uric acid levels were taken twice, before and after the induction of potassium oxonate. Blood was drawn four times to assess MDA levels: before the installation of potassium oxonate, after the inauguration of potassium oxonate, or on day 0 (Pre Test), day 14 (Post-test 1), and day 28. (Post-test 2). 1 ml of rat blood was extracted from the retro-orbital sinus. The enzymatic approach was used to determine blood uric acid levels utilizing uric acid FS reagent and the premise of enzymatic photometric test TBHBA (2,4,6 - tribromo - 3 - hydroxybenzoic acid). In contrast, MDA levels were examined by measuring Thio Barbuturic Acid Reactive Substance (TBARS) levels (Bridgers et al., 2010).

 ISSN 2502-4825 (print), ISSN 2502-9495 (online)

Data analysis

The data were statistically evaluated using SPSS version 25 and provided as mean SD. Statistical analysis was performed to determine the effect of differences in dose variations using a one-way ANOVA test, as well as statistical analysis to assess the impact of differences in duration of administration using a repeated measured ANOVA test and to determine the effect of the interaction of dose and duration of administration using a mixed design. The statistical significance value is p-value 0.05.

RESULTS AND DISCUSSION

After 15 days of calcium oxonate induction at a dosage of 250 mg/kg BW/day, uric acid levels demonstrated the effectiveness of hyperuricemia modelling, which was accompanied by elevated MDA levels. The P2 group had the most excellent mean uric acid levels at 8.28 mg/dL and the lowest in the P3 group at 8.03 mg/dL, whereas the KN group had the highest mean MDA levels at 10.20 nmol/mL and the weakest in the P1 group at 9.77 nmol/mL.

Table 1 Mean of uric acid and MDA examination before and after induction

Examination	Groups	*Mean* ± SD	
		Prior to Induction	Upon Induction
Asam Urat	KN	1,39 ± 0,97	8,13 ± 0,15
	P1	1,39 ± 0,94	8,04 ± 0,24
	P2	1,46 ± 0,79	8,28 ± 0,07
	P3	1,41 ± 1,22	8,03 ± 0,19
	P^b	0,659	0.080
MDA	KN	1,01 ± 0.11	10,21 ± 0,23
	P1	1,01 ± 0,14	9,77 ± 0,47
	P2	1.06 ± 0,13	10,20 ± 0,16
	P3	1.07 ± 0,10	9,99 ± 0,53
	P^b	0,62	0,195

Notes: KN: Negative Control; P1: 1.8ml/200gBW dose of red cabbage juice; P2: 3.6ml/200gBW dose of red cabbage juice; P3: 7.2ml/200gBW dose of red cabbage juice

The success of modelling is determined by the random allocation of rats and the selection of the male sex since they have no hormone estrogen. The estrogen hormone can aid in the excretion of uric acid through urine, allowing it to return to normal (Suhendi, 2011). Induction is performed using potassium oxonate, as described by Dhouibi et al. (2021), by injecting potassium oxonate intraperitoneally. The side effect of potassium oxonate induction is a decrease in endogenous antioxidant capacity, which causes oxidative stress by increasing the formation of ROS via enzymatic oxidation reactions via three main pathways, namely the xanthine oxidase system (XO) pathway, the NADPH-oxidase pathway, and the endothelial nitric oxide synthase (eNOS) enzyme system pathway (Hisatome et al., 2020). One was demonstrated in this study, in which the induction of potassium oxonate at a dosage of 250 mg/KgBB/day for 15 days caused hyperuricemia in the rat model, with an average rise in uric acid levels of 6.70 mg/dL and a substantial increase in MDA levels (Table 1). This demonstrates the importance of exogenous antioxidants in reducing oxidative damage caused by hyperuricemia.

MDA levels were assessed three times during the intervention: on day 0, day 14, and day 28. The intervention was administered in red cabbage juice at 1.8 ml/200g BW for group P1, 3.6 ml/200g BW for group P2, and 7.2 ml/200g for group P3. Table 2 depicts the changes in mean MDA levels according to dosage and time.

Table 2: Mean Pre and Post MDA Examination

Groups	*Mean* ± SD(g)			P^b
	0^{th} day (*Pre*)	14^{th} day (*Post* 1)	28^{th} Day (*Post* 2)	
KN	10,20 ± 0,23	10,40 ± 0,19	10,54 ± 0,22	0,001*
P1	9,77 ± 0,47	7,78 ± 0,31	5,57 ± 0,23	0,001*
P2	10,21 ± 0,16	7,02 ± 0,16	4,15 ± 0,24	0,001*
P3	9,99 ± 0,53	6,03 ± 0,55	3,02 ± 0,15	0,001*
P^a	0,195	0,001*	0,001*	
			P-Interaksi	0,001

Notes: Pa: One-way ANOVA-post hoc Tukey; Pb: Repeated measures ANOVA; P-Interaction: Analysis using Repeated Measure ANOVA Test with mixed design *There is a significant difference (p<0.05)

From Table 2, based on the dose of administration between groups, there were significant differences on day 14 and day 28 (p<0.05). A comparison of dose variations between all groups can be found in Table 3. The mean MDA levels of the red cabbage juice intervention group (P1-3) differed significantly from the KN group on days 14 and 28. The P1 group had nearly the same levels as the P2 group on day 14; however, there was still a significant. Compared to the control group, The reduction in MDA levels was most substantial in P3, which received red cabbage juice at a dosage of 7.2 ml/200g BW. On the 28th day of observation, the average MDA level of the P3 group exhibited the most significant decline of all groups.

Table 3. Comparison of Mean MDA Levels by Doses

Groups	△ Day 14 MDA Level	*P*	△ Day 28 MDA Level	*P*
KN dan P1	2,62 ± 0,12	0,001	4,97 ± 0,01	0,001
KN dan P2	3,38 ± 0,03	0,001	6,39 ± 0,02	0,001
KN dan P3	4,37 ± 0,36	0,001	7,52 ± 0,07	0,001
P1 dan P2	0,76 ± 0,01	0,005	1,42 ± 0,01	0,001
P1 dan P3	1,75 ± 0,24	0,001	2,55 ± 0,08	0,001
P2 dan P3	0,99 ± 0,39	0,001	1,13 ± 0,09	0,001

Note: P: *One way anova-post hoc tukey*

Table 2 also informs the effect of the duration of administration on MDA levels in all groups. Although there was a significant difference (p 0.05) in the KN group that did not get any treatment, the MDA levels hardly changed (approximately 10), and the difference in decline was less than 0.5 g, while in the treatment group showed a significant decrease as shown in Table 4. The mean MDA levels seen from the duration of administration explained that the P3 group tended to experience the highest decrease among other treatment groups, namely the P1 and 2 groups, on day 14 and day 28 of intervention.

Table 4. Comparison of Mean MDA Levels Based on Time Duration

Groups	Times	△ MDA (Mean ± SD (nmol/dL)	*P*
	Day 0 and day 14	0,20 ± 0,04	0,001
KN	Day 0 and day 28	0,34 ± 0,01	0,001
	Day 14 and day 28	0,14 ± 0,03	0,001
	Day 0 and day 14	-1,98 ± 0,16	0,001
P1	Day 0 and day 28	-4,20 ± 0,24	0,001
	Day 14 and day 28	-2,21 ± 0,08	0,001
	Day 0 and day 14	-3,17 ± 0,00	0,001
P2	Day 0 and day 28	-6,04 ± 0,08	0,001
	Day 14 and day 28	-2,87 ± 0,08	0,001
	Day 0 and day 14	-3,90 ± 0,02	0,001
P3	Day 0 and day 28	-6,97 ± 0,38	0,001
	Day 14 and day 28	-3,01 ± 0,40	0,001

Note: P : *Reapeted Measured Anova-post hoc tukey*

The interaction of dose and duration of administration also showed significant differences (p<0.05) between groups (Table 2). As shown in Figure 4.1, dose groups P1 and 3 had the same impact on lowering MDA levels on day 2. On day 5, the dosage of group P1 had the same impact as group P2. The value of the decline is yet unknown because it is beyond the scope of researchers' observation. Similarly to the previous conclusion, the P3 group had the most remarkable decrease in this test.

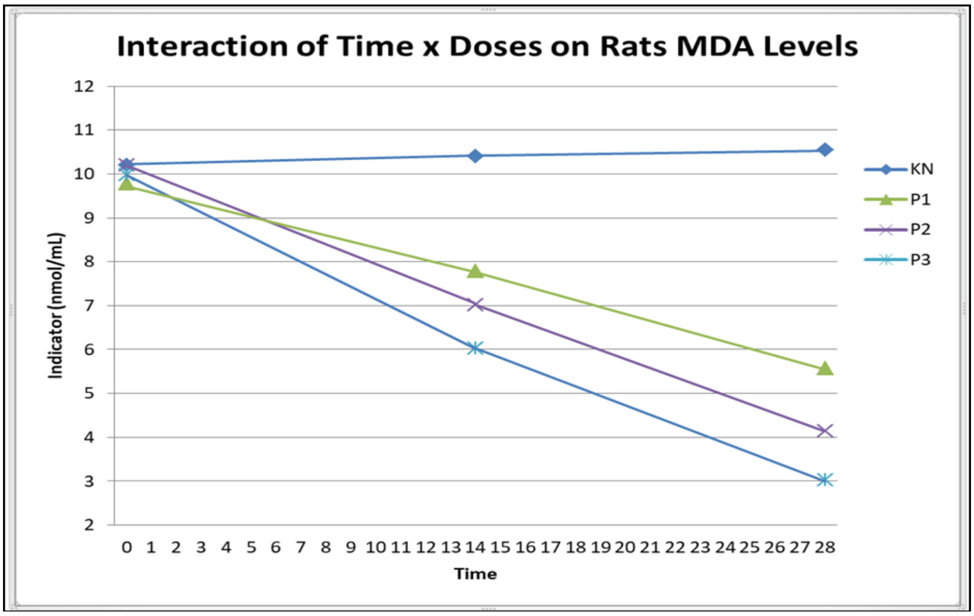

Figure 1. MDA levels in rats treated with red cabbage juice. Each row represents one of four distinct groups. The data are presented as standard deviations of the mean and analyzed using Repeatedly Measured ANOVA.

 ISSN 2502-4825 (print), ISSN 2502-9495 (online)

Among the other dosages, the analytical test revealed that providing red cabbage juice at a dose of 7.2ml/200gr BW had the most dominant effect on lowering MDA levels. Intervention within 14 days lowered MDA levels by 3.90 nmol/dL, and this trend continued until day 28, reaching 6.97 nmol/dL. Increasing the dose in the research seeks to find the adequate amount but must still consider the toxicity implications (Chinedu et al., 2013). It is worth noting that the usage of dosages in this study did not result in abnormalities in rats, such as weakness, prolonged sleep, coma, or death, until the conclusion of the intervention. According to Cruz et al. 2016, providing red cabbage water extracts at a dosage of 500 mg/kg twice daily provides a hypolipidemic effect in hyperlipidemic rats without harm. According to FDA 2022 standards, any drug is deemed a low-level potential hazard when the oral dosage is more significant than 2000 mg/kg BW, and the fatal toxicity among the tested rats is less than 50%. As a result, this study's administration of red cabbage juice in varied amounts was safe.

Red cabbage juice is a vegetable that has high antioxidant activity (Cruz et al., 2016; Lukitasari, 2017). Anthocyanins are the most potent antioxidants, supplying purplish red pigments that are good for health. (Ghareaghajlou et al., 2021; Podsędek et al., 2006). According to preliminary research, 100g of red cabbage contains 283 mg of anthocyanins or 2.8%. Because of the qualities of anthocyanins in red cabbage juice, the mechanism of the beneficial effect happened in all treatment groups. The P1 and 2 therapy groups significantly decreased MDA levels by an average of 4-6nmol/dL.

Further proof is that in the P3 group, the administration of 7.2ml/200g BW was able to reduce MDA levels to normal limits on the 28th day of intervention (< 4nmol/mL). The mechanism of anthocyanin compounds acts both directly and indirectly to lower MDA levels. Presently, by collecting ROS and providing electrons to bind, as well as indirectly, by stimulating antioxidant enzymes, blocking prooxidant enzymes, and creating phase II detoxifying enzymes and antioxidant enzymes (Situmorang & Zulham, 2020). According to numerous ideas, it is explained that oxidative stress can cause lipid peroxidation reactions, proteins including enzymes and DNA. If this condition continues, cell damage and death will occur. With a decrease in oxidative stress, oxidative stress-related diseases can be inhibited due to antioxidant and anti-inflammatory activities (Hassan & Samah et al., 2013).

LIMITATION OF THE STUDY

The study's limitation is that we did not undertake a renal histopathology test to detect glomerular injury and tubular ischemia caused by increased oxidative stress due to elevated uric acid levels.

CONCLUSIONS AND SUGGESTIONS

Red cabbage juice reduces oxidative stress in hyperuricemia rats by lowering MDA levels. This is demonstrated by administering a 7.2 ml/200gr BW on day 28, which can lower MDA levels to normal. While dosages of 1.8 and 3.6 ml/200g BW can lower MDA levels, they remained under oxidative stress conditions on days 14 and 28. The effective dosage to lower MDA levels in this investigation was 7.2 ml/200g BW.

Acknowledgment

We would like to thank the researchers from Gadjah Mada University's Center for Food and Nutrition Studies Laboratory (CFNS) in Yogyakarta for their assistance.

ETHICAL CONSIDERATION

This research protocol has received an ethical approval issued by the Health Research Ethics Committee Faculty of Medicine, Universitas Sebelas Maret No:83/UN27.06.11/KEP/EC/2022.

Funding Statement

No funding from any research grant.

Conflict of Interest Statement

The author declares that there is no conflict of interest.

REFERENCES

Ab, A. (2017). Sample Size Calculation for Animal Studies Using Degree of Freedom (E); an Easy and Statistically Defined Approach for Metabolomics and Genetic Research. *Current Trends in Biomedical Engineering & Biosciences*, *10*(2). https://doi.org/10.19080/CTBEB.2017.10.555785.

Alappat, B., & Alappat, J. (2020). Anthocyanin Pigments: Beyond Aesthetics. *Molecules*, *25*(23), 5500. https://doi.org/10.3390/molecules25235500.

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., Birnbaum, N. S., Burmester, G. R., Bykerk, V. P., Cohen, M. D., Combe, B., Costenbader, K. H., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J. M. W., Hobbs, K., Huizinga, T. W. J., Kavanaugh, A., … Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatism*, *62*(9), 2569–2581. https://doi.org/10.1002/art.27584.

Ali, S. S., Ahsan, H., Zia, M. K., Siddiqui, T., & Khan, F. H. (2020). Understanding oxidants and antioxidants: Classical team with new players. *Journal of Food Biochemistry*, *44*(3). https://doi.org/10.1111/jfbc.13145.

Bahorun, T., Luximon-Ramma, A., Crozier, A., & Aruoma, O. I. (2004). Total phenol, flavonoid, proanthocyanidin and vitamin C levels and antioxidant activities of Mauritian vegetables. *Journal of the Science of Food and Agriculture*, *84*(12), 1553–1561. https://doi.org/10.1002/jsfa.1820.

Bridgers, E. N., Chinn, M. S., & Truong, V.-D. (2010). Extraction of anthocyanins from industrial purple-fleshed sweetpotatoes and enzymatic hydrolysis of residues for fermentable sugars. *Industrial Crops and Products*, *32*(3), 613–620. https://doi.org/10.1016/j.indcrop.2010.07.020.

BPOM. (2022). Pedoman Uji Toksisitas Nonklinik secara in vivo. *Peraturan Kepala Badan Pengawas Obat dan Makanan Republik Indonesia No. 10 Tahun 2022*.

Cha, R., Kim, S. H., Bae, E. H., Yu, M., Choi, B. S., Choi, H. Y., Kang, S. W., Shin, J., Han, S. Y., Yang, C. W., & Kang, D.-H. (2019). Physicians′ perceptions of asymptomatic hyperuricemia in patients with chronic kidney disease: A questionnaire survey. *Kidney Research and Clinical Practice*, *38*(3), 373–381. https://doi.org/10.23876/j.krcp.19.007.

Chinedu, E., Arome, D., & Ameh, F. (2013). A new method for determining acute toxicity in animal models. *Toxicology International*, *20*(3), 224. https://doi.org/10.4103/0971-6580.121674.

Cruz, A. B., Pitz, H. da S., Veber, B., Bini, L. A., Maraschin, M., & Zeni, A. L. B. (2016). Assessment of bioactive metabolites and hypolipidemic effect of polyphenolic-rich red cabbage extract. *Pharmaceutical Biology*, *54*(12), 3033–3039. https://doi.org/10.1080/13880209.2016.1200633.

Deng, L., Du, C., Song, P., Chen, T., Rui, S., Armstrong, D. G., & Deng, W. (2021). The Role of Oxidative Stress and Antioxidants in Diabetic Wound Healing. *Oxidative Medicine and Cellular Longevity*, *2021*, 1–11. https://doi.org/10.1155/2021/8852759.

Dhouibi, R., Affes, H., Salem, M. B., Moalla, D., Marekchi, R., Charfi, S., Hammami, S., Sahnoun, Z., Jamoussi, K., Zeghal, K. M., & Ksouda, K. (2021). Creation of an adequate animal model of hyperuricemia (acute and chronic hyperuricemia); study of its reversibility and its maintenance. *Life Sciences*, *268*, 118998. https://doi.org/10.1016/j.lfs.2020.118998.

Eleftheriadis, T., Golphinopoulos, S., Pissas, G., & Stefanidis, I. (2017). Asymptomatic hyperuricemia and chronic kidney disease: Narrative review of a treatment controversial. *Journal of Advanced Research*, *8*(5), 555–560. https://doi.org/10.1016/j.jare.2017.05.001.

Fabbrini, E., Serafini, M., Colic Baric, I., Hazen, S. L., & Klein, S. (2014). Effect of Plasma Uric Acid on Antioxidant Capacity, Oxidative Stress, and Insulin Sensitivity in Obese Subjects. *Diabetes*, *63*(3), 976–981. https://doi.org/10.2337/db13-1396.

Fitriyah, P. C., Juanita, F., & Mudayan, A. (2011). Hubungan Obesitas Dengan Kadar Asam Urat Darah Di Dusun Pilanggadung Kecamatan Tikung Kabupaten Lamongan. *Jurnal Surya*, 2(9).

Forman, H. J., & Zhang, H. (2021). Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. *Nature Reviews Drug Discovery*, *20*(9), 689–709. https://doi.org/10.1038/s41573-021-00233-1

Franke, A. A., Custer, L. J., Arakaki, C., & Murphy, S. P. (2004). Vitamin C and flavonoid levels of fruits and vegetables consumed in Hawaii. *Journal of Food Composition and Analysis*, *17*(1), 1–35. https://doi.org/10.1016/S0889-1575(03)00066-8.

Ghareaghajlou, N., Hallaj-Nezhadi, S., & Ghasempour, Z. (2021). Red cabbage anthocyanins: Stability, extraction, biological activities and applications in food systems. *Food Chemistry*, *365*, 130482. https://doi.org/10.1016/j.foodchem.2021.130482.

Hassan, F. A., & Samah, A. A. (2015). 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. International Journal of Advanced Research, 2(6), 55–61. ISSN 2320-5407.

Hisatome, I., Li, P., Taufiq, F., Maharani, N., Kuwabara, M., Ninomiya, H., & Bahrudin, U. (2020). Hyperuricemia as a Risk Factor for Cardiovascular Diseases. *Journal of Biomedicine and Translational Research*, *6*(3), 101–109. https://doi.org/10.14710/jbtr.v6i3.9383.

Kumar, B., & Lenert, P. (2016). Gout and African Americans: Reducing disparities. *Cleveland Clinic Journal of Medicine*, *83*(9), 665–673. https://doi.org/10.3949/ccjm.83a.15133.

Lukitasari, D. M., Indrawati, R., Chandra, R. D., Heriyanto., & Limantara, L. (2017). Mikroenkapsulasi Pigmen Dari Kubis Merah: Studi Intensitas Warna Dan Aktivitas Antioksidan. *Jurnal Teknologi dan Industri Pangan*, 28(1), 1-9. https://doi: 10.6066/jtip.2017.28.1.1.

Maiuolo, J., Oppedisano, F., Gratteri, S., Muscoli, C., & Mollace, V. (2016). Regulation of uric acid metabolism and excretion. *International Journal of Cardiology*, *213*, 8–14. https://doi.org/10.1016/j.ijcard.2015.08.109.

Podsędek, A., Sosnowska, D., Redzynia, M., & Anders, B. (2006). Antioxidant capacity and content of Brassica oleracea dietary antioxidants. *International Journal of Food Science and Technology*, *41*(s1), 49–58. https://doi.org/10.1111/j.1365-2621.2006.01260.x.

Renaudin, F., Orliaguet, L., Castelli, F., Fenaille, F., Prignon, A., Alzaid, F., Combes, C., Delvaux, A., Adimy, Y., Cohen-Solal, M., Richette, P., Bardin, T., Riveline, J.-P., Venteclef, N., Lioté, F., Campillo-Gimenez, L., & Ea, H.-K. (2020). Gout and pseudo-gout-related crystals promote GLUT1-mediated glycolysis that governs NLRP3 and interleukin-1β activation on macrophages. *Annals of the Rheumatic Diseases*, *79*(11), 1506–1514. https://doi.org/10.1136/annrheumdis-2020-217342.

Sebastian, R. S., Wilkinson Enns, C., Goldman, J. D., Martin, C. L., Steinfeldt, L. C., Murayi, T., & Moshfegh, A. J. (2015). A New Database Facilitates Characterization of Flavonoid Intake, Sources, and Positive Associations with Diet Quality among US Adults. *The Journal of Nutrition*, *145*(6), 1239–1248. https://doi.org/10.3945/jn.115.213025.

Sharaf El Din, U. A. A., Salem, M. M., & Abdulazim, D. O. (2017). Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. *Journal of Advanced Research*, *8*(5), 537–548. https://doi.org/10.1016/j.jare.2016.11.004.

Situmorang, N., & Zulham, Z. (2020). MALONDIALDEHYDE (MDA) (ZAT OKSIDAN YANG MEMPERCEPAT PROSES PENUAAN). *JURNAL KEPERAWATAN DAN FISIOTERAPI (JKF)*, *2*(2), 117–123. https://doi.org/10.35451/jkf.v2i2.338.

Suhendi, A. (2011). Aktivitas antihiperurisemia ekstrak air jinten hitam (Coleus ambonicus Lour) pada mencit jantan galur balb-c dan standardisasinya. *Majalah Farmasi Indonesia*, 22(2), 77–84.

Wu, X., Beecher, G. R., Holden, J. M., Haytowitz, D. B., Gebhardt, S. E., & Prior, R. L. (2004). Lipophilic and Hydrophilic Antioxidant Capacities of Common Foods in the United States. *Journal of Agricultural and Food Chemistry*, *52*(12), 4026–4037. https://doi.org/10.1021/jf049696w.

Wulandari, A., Dirgahayu, P., & Wiboworini, B. (2021). Anti-hyperurisemic Activity of Combination of Beetroot Powder (Beta vulgaris L.) And Allopurinol in Potassium Oxonate-Induced White Rats. *Indonesia Journal of Biomedical Science*, *15*(2), 164–168. https://doi.org/10.15562/ijbs.v15i2.319