# The Effect of Red Dragon Fruit (*Hylocereus polyrhizus*) Juice on Leptin Levels in Overweight Model of *Sprague Dawley Rats*

**Novia Zuriatun Solehah, Herviana*, Nissa Anggriany, Karina Anindita**

Departmen of Nutrition, Universitas Bumigora, Mataram, Nusa Tenggara Barat, Indonesia

**ABSTRACT**

**Background:** Obesity is strongly linked to elevate leptin levels and oxidative stress, both of which contribute to the development of various metabolic disorders. Leptin, a hormone that regulates metabolism and appetite, becomes less effective in obese individuals due to leptin resistance, thereby exacerbating metabolic dysfunction.

**Objective:** This study aims to evaluate the effect of red dragon fruit (*Hylocereus polyrhizus*) juice on leptin levels in *Sparague Dawley rats* using an overweight model.

**Method:** This experimental study used a pre-post test control group design and involved six treatment groups , including a normal group, a negative control group, a positive control group (orlistat), and three treatment groups receiving different doses of red dragon fruit juice (3.5 g, 7 g, and 10.5 g per 200 g body weight). The intervention was carried out for 14 days following a 14- day induction of obesity using a high-fat and high-carbohydrate diet. Leptin levels were measured before and after the intervention. Leptin examination was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) method, and all data were analyzed using paired t-test, one-way ANOVA, and post hoc tests with a significance level of $p < 0.05$.

**Results:** The results showed that administration of red dragon fruit juice significantly reduced leptin levels ($p<0.001$) in all treatment groups. The greatest reduction was observed in the group receiving the 10.5 g dose, with an average decrease of 75.03%, which was nearly equivalent to the orlistat group that reduced leptin levels by 79.93%.

**Conclusion:** Red dragon fruit juice has the potential to serve as a non-pharmacological agent in reducing leptin levels and oxidative stress under obesity conditions, with an effectiveness approaching that of orlistat.

***Keywords:*** *red dragon fruit juice; leptin; obesity; Sprague Dawley rats;*



## BACKGROUND

Obesity affects individuals of all age groups, from children and adolescents to adults. This condition disrupts the balance between metabolic and immune functions, contributing to degenerative diseases such as diabetes mellitus, atherosclerosis, coronary heart disease, hypertension, and metabolic syndrome. It is strongly associated with increased mortality rates globally.[1] The World Health Organization (WHO) reported that the prevalence of obesity in 2016 increased threefold (1.9 billion) of the world's population, and it is estimated that more than 42 million people with obesity will increase to 70 million by 2025.[2,3] In Indonesia, the prevalence of obesity rose from 14.8% in 2013 to 21.8% in 2018.[4] The condition of obesity affects an individual's leptin secretion. Leptin is a hormone produced by adipose (fat) tissue and plays an important role in regulating metabolism and appetite. Elevated leptin levels indicate an increase in body fat. In individuals with obesity, blood leptin levels can reach 100 ng/mL.[5] Studies have shown that individuals with obesity have higher leptin levels compared to those with normal body weight.[6] Another study conducted by Stoner et al. (2013) reported that overweight children and adolescents experience increased levels of leptin, IL-6, TNF-α, and CRP, as well as a greater decrease in adiponectin compared to those with normal body weight. This increase in leptin levels is not only associated with energy regulation but also plays a role in oxidative stress mechanisms in individuals with obesity.

Obesity induces oxidative stress as a result of an imbalance between pro-oxidants and endogenous antioxidants.[7] This imbalance facilitates the excessive production of reactive oxygen species (ROS).[8] Malondialdehyde (MDA) is one of the most widely recognized biomarkers of oxidative stress, and its concentration in the blood serves as a reliable indicator of elevated oxidative damage.[9] Consequently, strategies aimed at reducing oxidative stress represent a crucial component in the clinical management of obesity.

Obesity management involves not only pharmacological therapy but also non-pharmacological approaches. Non-pharmacological management includes lifestyle modifications such as increasing physical activity, weight reduction, limiting sodium intake, avoiding alcohol consumption, and increasing the intake of fruits and vegetables. Research has shown a positive correlation between the consumption of fruits and

vegetables rich in fiber, flavonoids, carotenoids, vitamins, and minerals and the reduction of inflammation and oxidative stress. One fruit known to contain natural antioxidants, such as betacyanin, flavonoids, polyphenols, lycopene, and vitamins C, B1, B3, B12, along with beta-carotene, fiber, and the mineral phosphorus is red dragon fruit.[10] In 100 grams of red dragon fruit, the antioxidant activity is 67.45 ppm. A compound is considered to have good antioxidant activity if the $IC_{50}$ value is less than 200 ppm. In addition, other antioxidants found in red dragon fruit pulp include flavonoids at 35.26 ppm and anthocyanins at 8.8 g. Flavonoids help inhibit ROS by suppressing the activity of the enzymes xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH), thereby preventing oxidation reactions that produce free radicals.[11] Research has shown that administration of red dragon fruit extract at a dose of 500 mg/kg body weight has a significant effect on reducing oxidative stress markers.[12]

An alternative way to consume fruit is by processing it into fruit juice, which can provide similar health benefits.[13] Meta-analysis has shown that drinking half to one glass of unsweetened fruit juice can be an alternative for individuals who are unable to consume whole fruits.[14] Preparing fruit juice using a blender is considered more beneficial than using a juicer, as blending does not leave any part of the fruit unused. Therefore, consuming blended fruit juice is considered equivalent to consuming whole fruit.[10,15]

Based on the explanation above, further research is needed to examine the potential of red dragon fruit juice in reducing leptin levels in an obesity rat model. To date, the use of fruits—particularly red dragon fruit—to lower leptin levels has not been extensively investigated. Red dragon fruit was selected due to its high content of natural antioxidants, which are expected to serve as an alternative beverage capable of reducing free radicals in individuals with overweight and obesity

## MATERIALS AND METHODS

### Reaserch Design, Place, and Time

This study is experimental research used a pre-test and post-test control group design. It involved six treatment groups assigned through simple randomization, consisting of a normal group, a negative control group (NC) given a high-fat, high-carbohydrate diet, a positive control group (PC) given orlistat at a dose of 6.48 mg/200 g body weight. The samples in this study were Sprague Dawley rats aged 8–12 weeks, with a body weight of 150–200 g. The research was conducted at the Laboratory of the Center for Food and Nutrition Studies (PSPG PAU), Gadjah Mada University, Yogyakarta. The study was carried out over a period of 28 days.

### Preparation of Dragon Fruit

The dosage of red dragon fruit juice administered was based on a therapeutic dose previously tested in humans, which is 200 ml of fruit juice obtained from 100 g of fruit.[16] The maximum volume of liquid administration for rats weighing 200 grams is 5 ml. The dosage used refers to the study by Karimah et al. (2014), which found that 7.2 ml of dragon fruit juice was effective in reducing cholesterol levels. In the present study, the dose was rounded down to 7 ml to assess the effectiveness of a slightly lower dose.[17] Based on these considerations, the calculated dosage is as follows 0.5 × 7 ml = 3.5 ml/200gBW (dose 1), 7 ml/200gBW (dose 2), 1.5 × 7 ml = 10.5 ml (dose 3)

### Animal Experimental Design

This study used Sprague Dawley rats obtained form the Nutrition Laboratory of the Center for Food and Nutrition Studies of Gadjah Mada University (PSPG PAU UGM) Yogyakarta. The sample amounted to 30 with the inclusion criteria of male Rattus Novergicus Sprague Dawley rats, 8-12 weeks of age, body weight 150-200 grams, and healthy conditions and active movements. Samples were divided into 6 groups, namely:

**Table 1 Treatment groups**

| Group | Treatment |
|---|---|
| Normal group (N) | Healthy rats were given standard diet ad libitium for 14 days |
| Negative control group (KN) | Obese rats were given standard diet ad libitium for 14 days |
| Positive control group (KP) | Obese rats were given orlistat 6.48 mg/200gBW for 14 days |
| Treatment group 1 (P1) | Obese rats were given dragon fruit 3.5 ml/200gBW for 14 days |
| Treatment group 2 (P2) | Obese rats were given dragon fruit 7 ml/200gBW for 14 days |
| Tratment group 3 (P3) | Obese rats were given dragon fruit 10.5ml/200gBW for 14 days |

All experimental rats were acclimatized for 3 days in individual cages and provided with standard Comfeed diet and drinking water ad libitum. The average feed requirement for rats is 5 g/100 g BW/day.[18] The rats were housed in plastic cages measuring 25 cm × 15 cm × 7 cm, with one rat placed in each cage. The animals were maintained in a controlled environment using hygienic polypropylene cages, in a dedicated

animal room with temperature control (20–27°C), a 12-hour light and 12-hour dark cycle (lights on at 07:00 WIB), and humidity maintained at 40–60%. The rats were considered to be in stable condition when their feed and water intake met their physiological requirements.[19,20,21] The composition of the standard Comfeed diet is presented in Table 2.

**Table 2 Composition of Standard Comfeed Diet**

| Component | Content |
|---|---|
| Energy | 315-355 calories |
| Carbohydrates | 53-57% |
| Moisture | Max 12% |
| Crude Protein | Min 15% |
| Crude Fat | 3-7% |
| Crude Fiber | Max 6% |
| Ash | Max 7% |
| Calcium | 0.9-1.1% |
| Phosphorus | 0.6-0.9% |

Source : Modified from Budianto (2015)

**Body Weight Measurement of Experimental Animals**

Body weight measurements were conducted using a container, in which the container was weighed first. The rat was then placed inside the container, and the combined weight of the container and the rat was recorded. A digital scale with an accuracy of 0.1 g was used for all measurements. The body weight of each rat was obtained by subtracting the weight of the container from the total weight. If a rat weighed below the required criteria (150–200 g), it was replaced with another rat that met the inclusion criteria to ensure homogeneity of body weight across groups. Body weight measurements were conducted in three stages: after the 3-day acclimatization period, during the obesity induction process (measured weekly to monitor weight gain), and prior to termination of the animals.

**Indicators for Determining Obesity in Rats**

Obesity in rats was determined using the Lee Index as the primary indicator. Rats were classified as obese if their Lee Index value exceeded 300. Body weight was measured using a digital scale, while body length was measured using a ruler. The Lee Index was calculated by comparing body weight and body length.

**Leptin Measurement**

Leptin levels were measured using the Rat LEP ELISA Kit (Elabscience Biotechnology). Plasma samples were used for the analysis.

**Data Analysis**

The data obtained will be analyzed for normality using the Saphiro Wilk test. Bivariate analysis uses ANOVA if the data is normally distributed and if the results obtained are significant. Data analysis using SPSS software version 16.

**Ethical Clearance**

This study has been declared fearible and passed the ethical test by the Ethics Commission of the Faculty of Medicine, Sebelas Maret University with number No.23/UN27.06.6.1/KEP/EC/2024

**RESULTS**

Changes in leptin before and after the intervention in each group are presented in Table 1.

**Table 1. Results of Leptin Level Examination**

| Variable | H1 (Average ± SD) | H14 (Average ± SD) | Δ (+) | Δ (%) | p [a] |
|---|---|---|---|---|---|
| **Leptin (ng/ml)** | | | | | |
| **KN** | 9.41 ± 0.39 | 9.64 ± 0.37 | 0.23 | 2.55 | <0.001 |
| **KP** | 9.30 ± 0.39 | 2.09 ± 0.07 | -7.21 | -79.93 | <0.001 |
| **P1** | 9.20 ± 0.34 | 5.88 ± 0.30 | -3.32 | -37.56 | <0.001 |
| **P2** | 9.33 ± 0.45 | 3.79 ± 0.34 | -5.54 | -59.96 | <0.001 |
| **P3** | 9.19 ± 0.39 | 2.52 ± 0.38 | -6.67 | -75.03 | <0.001 |
| **p** | 0.876[b] | <0.001[b] | | | |

Data are presented as mean ± SD. K = Normal rat group; NC = Obesity + HFHC diet; PC = Obesity + orlistat 6.48 mg/200 g BW; T1 = Obesity + red dragon fruit juice at 3.5 g/200 g BW; T2 = Obesity + red dragon fruit juice at 7 g/200 g BW; T3 = Obesity + red dragon fruit juice at 10.5 g/200 g BW.ma). a) Paired t-test was used to analyze pre- and post-test differences within groups. b) One-Way ANOVA was used to analyze differences between groups. Statistical significance was set at $p < 0.05$. Δ (+) value = difference in body weight before and after the intervention. Δ (%) value = percentage change in body weight before and after the intervention. H1= Day1, H14=Day14.

Table 1 presents the changes in leptin levels (ng/mL) from day 1 (H1) to day 14 (H14) across all study groups. The negative control group (KN) showed a slight increase in leptin levels (+0.23 ng/mL; +2.55%), which was statistically significant ($p < 0.001$). In contrast, the positive control group (KP) and all intervention groups (P1, P2, and P3) experienced substantial reductions in leptin levels. The largest decrease was observed in the KP group (–7.21 ng/mL; –79.93%), followed by P3 (–6.67 ng/mL; –75.03%), P2 (–5.54 ng/mL; –59.96%), and P1 (–3.32 ng/mL; –37.56%). All reductions were statistically significant ($p < 0.001$). Between-group comparison showed no significant difference at baseline ($p = 0.876$), but significant differences were observed on day 14 ($p < 0.001$), indicating that the intervention produced differentiated effects on leptin reduction across groups.

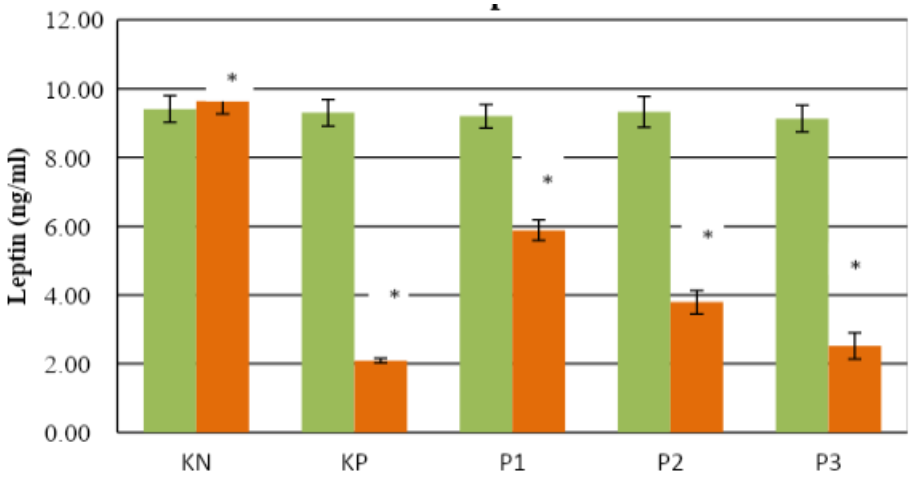


Figure 1. Changes in Leptin before and after the intervention

Figure 1. Changes in leptin concentrations before and after the intervention across all study groups. The green bars represent baseline leptin levels, while the orange bars indicate levels measured after 14 days of intervention. Minimal change was observed in the negative control group, whereas the positive control and all treatment groups showed substantial reductions in leptin concentrations.

## DISCUSSION

This study demonstrated that the administration of red dragon fruit juice significantly reduced leptin levels in overweight Sprague Dawley rats. The greatest decrease in leptin levels was observed in the group receiving a dose of 10.5 g/200 g BW, with a reduction of 75.03%, which was comparable to the positive control group (orlistat), showing a reduction of 79.93%. These findings indicate that red dragon fruit juice has potential as a non-pharmacological therapy for managing obesity and related metabolic disorders. Leptin is a hormone produced by adipose tissue and plays a key role in regulating energy balance. In obesity, leptin levels increase, yet the body develops leptin resistance, leading to impaired appetite regulation. Elevated leptin levels can also contribute to oxidative stress through increased production of reactive oxygen species (ROS).

Red dragon fruit contains various bioactive compounds such as betacyanins, flavonoids, polyphenols, lycopene, and vitamin C, all of which function as antioxidants. These compounds play an important role in reducing ROS levels and improving leptin sensitivity. Previous studies by Putri et al. (2021) and Zahra et al.

(2019) reported that consumption of red dragon fruit or its extract can decrease oxidative stress biomarkers such as MDA and enhance metabolic status in experimental animals.[22,12] These findings are consistent with those of Fadlilah et al. (2021), who demonstrated that red dragon fruit juice can reduce cholesterol levels.[23] Its effectiveness was found to be comparable to that of orlistat; however, red dragon fruit juice offers an advantage as it is derived from natural ingredients and does not cause the gastrointestinal side effects commonly associated with orlistat use.[24] In addition, the fiber content in red dragon fruit contributes to weight reduction and improves lipid profiles by reducing fat absorption. The flavonoids it contains also act as radical scavengers and enhance antioxidant enzyme activity through the Nrf2 signaling pathway.[25]

The findings of this study also indicate that the effectiveness of red dragon fruit juice is nearly comparable to that of orlistat in reducing leptin levels and ROS, but without the gastrointestinal side effects. Leptin resistance in obesity is associated with chronic oxidative stress, which disrupts leptin signaling pathways in the hypothalamus.[26] Antioxidants derived from fruits may help restore these pathways.[27] Betacyanins in red dragon fruit not only function as antioxidants but also inhibit the expression of inflammatory molecules such as TNF-α and IL-6.[28] Additionally, the fiber content of red dragon fruit enhances satiety, slows gastric emptying, and promotes the production of short-chain fatty acids (SCFAs), which benefit energy metabolism through the activation of GPR41 and GPR43.[29]

Several studies have also shown that foods rich in flavonoids and dietary fiber can reduce inflammation and improve oxidative status.[30] This supports the present findings indicating that red dragon fruit juice effectively reduces both ROS and leptin levels simultaneously. Its effectiveness is comparable to that of orlistat, but without long-term side effects such as diarrhea and steatorrhea.[31] This makes red dragon fruit juice a safer and more acceptable alternative for long-term use. Consumption of whole fruits or fruit juices has also been shown to reduce the risk of obesity, insulin resistance, and dyslipidemia, making the findings of this study highly relevant for promoting local food–based dietary patterns.[32]

Study Sistilli et al. (2021) showed that a natural phytonutrient-based approach is now increasingly used, fruits and vegetables rich in antioxidants can reduce the expression of inflammatory genes and improve the sensitivity of metabolic hormones.[33] Red dragon fruit juice also has potential as a prebiotic due to its fiber content, which can enhance beneficial bacteria and increase SCFA production, thereby reducing inflammation and improving leptin sensitivity.[34] Research by Putriningtyas et al. (2020) further supports that dragon fruit can improve cholesterol, blood glucose, and oxidative stress.[35,36] A meta-analysis by Wang et al. (2022) also found that the consumption of low-glycemic, antioxidant-rich fruits is associated with reductions in leptin, IL-6, and TNF-α.[37] This strengthens the hypothesis that red dragon fruit juice has the potential to improve leptin resistance. The observed decrease in leptin may also be related to the modulation of the AMPK and JAK-STAT pathways by polyphenols, as reported in recent studies.[38]

## CONCLUSION

The administration of red dragon fruit (*Hylocereus polyrhizus)* juice for 14 days was proven effective in reducing leptin levels and plasma Reactive Oxygen Species (ROS) in overweight-model *Sprague Dawley r*ats. The highest dose (10.5 g/200 g BW) resulted in the most significant decrease in leptin, showing an effect comparable to the positive control (orlistat). These findings indicate that red dragon fruit holds potential as a non-pharmacological intervention for managing obesity and oxidative stress. Its effectiveness is likely attributed to its natural antioxidant content, such as flavonoids, betacyanin, vitamin C, and soluble fiber, which contribute to anti-inflammatory activity and improved metabolic function. Additionally, red dragon fruit juice provides these benefits without the gastrointestinal side effects often associated with pharmacological treatments. Thus, red dragon fruit may serve as a natural, affordable, and safe alternative in the functional food-based management of obesity. However, further long-term studies and clinical trials in humans are needed to confirm its efficacy and safety in clinical settings.



## ACKNOWLEDGMENT

The author would like to express sincere gratitude to the Center for Food and Nutrition Studies, Universitas Gadjah Mada, for providing the facilities and support necessary for the completion of this research. Special thanks are also extended to all laboratory staff and individuals who assisted in the data analysis and intervention processes. The author greatly appreciates the moral and academic support from supervising lecturers and colleagues who contributed to the preparation of this manuscript. It is hoped that the results of this study will make a positive contribution to the advancement of nutrition science and public health.

## REFERENCES

1. Laksmita AS, Putu D, Vidika R, Widayanti NP. Deskripsi Tingkat Pengetahuan Masyarakat Denpasar terhadap Obesitas Lebih Rentan Terinfeksi COVID-19. J Muhammadiyah Med Lab Technol. 2023;2(6):130–42. https://doi.org/10.30651/jmlt.v6i2.17752
2. Khodaee GH, Saeidi M. Increases of Obesity and Overweight in Children : an Alarm for Parents and Policymakers. Int J Pediatr. 2016;4(28):1591–601. https://doi.org/10.22038/ijp.2016.6677
3. Rebello CJ, Kirwan JP, Greenway FL. Obesity, the most common comorbidity in SARS-CoV-2: is leptin the link? Int J Obes. 2020;44(9):1810–7. https://doi.org/10.1038/s41366-020-0640-5
4. Kemenkes RI. Laporan Nasional RISKESDAS. 2018;
5. Hoda MR, Theil G, Mohammed N, Fischer K, Fornara P. The Adipocyte-Derived Hormone Leptin Has Proliferative Actions on Androgen-Resistant Prostate Cancer Cells Linking Obesity to Advanced Stages of Prostate Cancer. J Oncol. 2012;2012:1–8. https://doi.org/10.1155/2012/280386
6. Cahyaningrum A. Leptin SebgI Indikator Obesitas. J Kesehat Prima. 2015;9(1):1364–71.
7. Yosika GF, Sukoco P, Pranoto A, Purwoto SP. Penurunan malondialdehyde serum setelah latihan interval dan continuous di pagi hari pada perempuan obesitas. J Sortif J Penelit Pembelajaran. 2020;6(2):288–303. https://doi.org/10.29407/js_unpgri.vi.14289
8. Susantiningsih T, Mustofa S. Ekspresi IL-6 dan TNF- α Pada Obesitas. J Kedokt Univ Lampung. 2018;2(2):174–80. https://doi.org/10.23960/jkunila.v2i2.pp174-180
9. Moazen M, Mazloom Z, Jowkar F, Nasimi N, Moein Z. Vitamin D, Adiponectin, Oxidative Stress, Lipid Profile, and Nutrient Intakes in the Females with Acne Vulgaris: A Case-Control Study. Galen Med J. 2019;8(2019):1–9. https://doi.org/10.31661/gmj.v8i0.1515
10. Kim Y. Quality of Fresh Vegetable and Fruit Juice produced with Low-Speed and High-Speed Juicers. Korean J Food Nutr. 2017;30(3):568–77. https://doi.org/10.7841/ksbbj.2014.29.3.145
11. Hardiningtyas SD, Purwaningsih S, Handharyani E. Aktivitas Antioksidan dan Efek Hepatoprotektif Daun bakau Api-Api Putih. J Pengolah Has Perikan Indones. 2014;17(1):80–91. https://doi.org/10.17844/jphpi.v17i1.8140
12. Zahra S, Pd M, Rosidi A. Pengaruh Pemberian Jus Buah Naga Merah (Hylocereus polyrhezeus) dan Aktifitas Fisik terhadap Kadar Kolesterol Total dan Kadar MDA. J Ilm SPIRIT. 2019;19(1):12–27. https://doi.org/10.36728/jis.v19i1.955
13. Imamura F, Connor LO, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages , artificially sweetened beverages , and fruit juice and incidence of type 2 diabetes : systematic review , meta-analysis , and estimation of population attributable fraction. BMJ. 2015;1–12. https://doi.org/10.1136/bmj.h3576
14. Murphy MM, Barrett EC, Bresnahan KA, Barraj LM. 100 % Fruit juice and measures of glucose control and insulin sensitivity: a systematic review and meta-analysis of randomised controlled trials. J Nutrutional Sci. 2017;6(59):1–15. https://doi.org/10.1017/jns.2017.63
15. Gouws CA, Georgouopoulou E, Mellor DD. The Effect of Juicing Methods on the Phytochemical and Antioxidant Characteristics of the Purple Prickly Pear ( Opuntia ficus indica )— Preliminary Findings on Juice and Pomace. Beverages. 2019;5(28):1–18. https://doi.org/10.3390/beverages5020028
16. Nisa FK, Ningtyias FW, Sulistiyani. Pengaruh Pemberian Jus Buah Naga merah (Hylocereus polyrhizus) terhadap Penurunan Tekanan Darah. 2019. 2019;3(1):12–8. https://doi.org/10.22487/ghidza.v3i1.15
17. Karimah F, Achmad S, Suganda RR. Efek Jus Buah Naga Super Merah (Hylocereus costaricensis) dan Simvastatin terhadap Kadar Kolesterol Total Darah dan Bobot Badan Tikus Jantan Galur Wistar Hiperkolesterolemia. Glob Med Heal Commun. 2014;2(2):79–84. https://doi.org/10.14710/jnc.v3i4.6865
18. Otto GM, Franklin CL, Clifford CB. Biology and Diseases of Rats Glen. Am Coll Lab Anim Med. 2020;151–207. https://doi.org/10.1016/B978-0-12-409527-4.00004-3
19. Lailani M, Edward Z, Herman RB. Gambaran Tekanan Darah Tikus Wistar Jantan dan Betina Setelah Pemberian Diet Tinggi Garam. J Kesehat Andalas. 2013;2(3):146–50. https://doi.org/10.25077/jka.v2i3.154
20. Widiartini W, Siswati Ek, Setiyawati A, Rohmah IM, Prasetyo E. Pengembangan Usaha Produksi Tikus Putih (Rattus norvegicus) Tersertifikasi dalam Upaya Memenuhi Kebutuhan Hewan Laboratorium. Pekan Ilm Mhs Nas Progr Kreat Mhs. 2013;
21. Palupi FD, Wasita B, Magna A, Nuhriawangsa P. Pengaruh Dosis dan Lama Pemberian EKstrak Etanol Pegagan (Centella asiatica) terhadap Kadar Gula Darah dan Derajat Insulitis Tikus Model Diabetes Melitus Tipe 2. MGMI. 2019;10(2):111–24. https://doi.org/10.22435/mgmi.v10i2.588
22. Putri MD, Wiboworini B, Dirgahayu P. Red dragon fruit juice in reducing ros levels and insulin

resistance In rats with type 2 diabetes mellitus model. J Gizi Indones. 2021;10(1):6–14. https://doi.org/10.14710/jgi.10.1.6-14
23. Fadlilah S, Sucipto A, Judha M, Amestiasih T, Dede C, Nekada Y. Red Dragon Fruit (Hylocereus Polyrhizus) to Reduce Cholesterol Level in People With Excessive Nutritional Status. Indian J Forensic Med Toxicol. 2021;15(4):2557–65. https://doi.org/10.37506/ijfmt.v15i4.17090
24. Ioannides-demos LL, Piccenna L, Mcneil JJ. Pharmacotherapies for Obesity : Past , Current , and Future Therapies. J Obes. 2011;2011:1–18. https://doi.org/10.1155/2011/179674
25. Rasyid HN, Orth MS, Ismiarto YD, Orth MS, Prasetia R, Orth MS. The Efficacy of Flavonoid Antioxidant from Chocolate Bean Extract : Prevention of Myocyte Damage Caused by Reperfusion Injury in Predominantly Anaerobic Sports. Malaysian Orthop J. 2012;6(3):3–6. https://doi.org/10.5704/moj.1207.012
26. Myers MG, Leibel RL, Seeley RJ, Schwartz MW. Obesity and Leptin Resistance: Distinguishing Cause from Effect. Trends Endocrinol Metab. 2011;21(11):643–51. https://doi.org/10.1016/j.tem.2010.08.002
27. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–61. https://doi.org/10.1172/jci21625
28. Esatbeyoglu T, Wagner AE, Schini-Kerth VB, Rimbach G. Betanin — A food colorant with biological activity. Mol Nutr Food Res. 2015;59(1):36–47. https://doi.org/10.1002/mnfr.201400484
29. Besten G Den, Eunen K Van, Groen AK, Venema K, Reijngoud D jan, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54:2325–40. https://doi.org/10.1194/jlr.r036012
30. Amiot MJ, Riva C, Vinet A. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. Obes Rev. 2016;17:573–86. https://doi.org/10.1111/obr.12409
31. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet. 2006;369(6):71–7. https://doi.org/10.1016/s0140-6736(07)60033-6
32. Boeing H, Bechthold A, Bub A, Ellinger S. Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr. 2012;(51):637–63. https://doi.org/10.1007/s00394-012-0380-y
33. Sistilli G, Kalendova V, Cajka T, Irodenko I, Bardova K, Oseeva M, et al. Krill Oil Supplementation Reduces Exacerbated Hepatic Steatosis Induced by Thermoneutral Housing in Mice with Diet-Induced Obesity. Nutrients. 2021;(13):1–24. https://doi.org/10.3390/nu13020437
34. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Shi Y, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science (80- ). 2018;1156(March):1151–6.
35. Putriningtyas ND, Permatasari I, Oktaviani D, Raha AS, Wahyuningsih S. Red dragon fruit (Hylocereus spp .) peel marmalade effectively improve blood glucose and lipid profile of hypercholesterolemic wistar rats. J Gizi Indones. 2020;9(1):61–7. https://doi.org/10.14710/jgi.9.1.61-67
36. Solehah NZ, Prayitno A, Pamungkasari EP. The Effect of Red Dragon Fruit (Hylocereus polyrhizus) on ROS Plasma of Overweight Sprague Dawley Rats. Media Gizi Indones. 2022;17(2):144–50. https://doi.org/10.20473/mgi.v17i2.144-150
37. Wang J, Liao B, Wang C, Zhong O, Lei X. Effects of Antioxidant Supplementation on Metabolic Disorders in Obese Patients from Randomized Clinical Controls: A Meta-Analysis and Systematic Review. Oxid Med Cell Longev. 2022;1–20. https://doi.org/10.1155/2022/7255413
38. Kumar V, Singh DD, Lakhawat SS, Yasmeen N, Pandey A, Singla RK. Biogenic Phytochemicals Modulating Obesity: From Molecular Mechanism to Preventive and Therapeutic Approaches. Evidence-Based Complement Altern Med. 2022;1–20. https://doi.org/10.1155/2022/6852276