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Sea Grapes Supplementation Can Reduce the Increase of Blood Sugar Levels in Male White Rats Given Toxic Doses of Paracetamol

(PENGIMBUHAN ANGGUR LAUT MAMPU MEREDAM KENAIKAN KADAR GULA DARAH TIKUS PUTIH JANTAN YANG DIBERI PARASETAMOL DOSIS TOKSIK)

Samsuri[1*], Rizky Salsabila Heryanto[2], Yudha Yaksa Crada Yoga Arum Raharjo[1] I Gusti Ayu Nadia Prasta Unique

[1]Department of Veterinary Pharmacology and Toxicology ,
[2]Bachelor Program of Veterinary Medicine,
Faculty of Veterinary Medicine, Universitas Udayana,
Jl Lingkar Kampus Unud Bukit Jimbaran,
Kuta, Badung, Bali, Indonesia, 80361.
*Email: samsuri@unud.ac.id

ABSTRACT

Paracetamol is an analgesic and can also function as antipyretic. Paraetamol is a drug widely used by the public, without considering its hepatotoxic potential which can affect blood sugar or glucose metabolism. On the other hand, sea grapes are rich in antioxidants. This study was aimed to determine the effect of *Caulerpa lentillifera* and paracetamol on the blood sugar levels of male white rats (*Rattus norvegicus*). Adult male white rats strain Wistar aged 3-4 months with an average weight of 160 g, were used in this study. A total of 25 head of rats, were divided into five treatment groups. Group I was given the same treatment but replaced with a placebo. Group II-V was given the same paracetamol at a dose of 250 mg/kg/BW/day. Sea grapes treatment on Group III was given 10 g/kg/BW/day, Group IV was given 15 g/kg/BW/day, and Group V was given 20 g/kg/BW/day. Induction materials (sea grapes and paracetamol) were administered orally afterward blood sugar levels were measured on the eleventh day using a glucometer. The results of the One way Analysis of variance test showed that sea grapes had a significant effect on blood sugar levels ($P \leq 0.01$). This proves that the antioxidant content in sea grapes actively influences changes in blood sugar levels due to paracetamol induction. Further statistical tests using the Duncan multiple range test indicated there was no significant difference ($P > 0.05$) in the different doses of sea grapes given. The presence of flavonoids in sea grapes, which are one of the catechin compounds, can provide the same antioxidant effect that can be achieved at lower doses.

Keywords: blood sugar level; *Caulerpa lentillifera*; paracetamol; white rat

ABSTRAK

Parasetamol adalah obat analgesik selain juga bisa berfungsi sebagai antipiretik. Obat parasetamol banyak digunakan oleh masyarakat dengan tanpa menghiraukan potensi hepatotoksiknya yang dapat memengaruhi metabolisme gula darah atau glukosa. Di sisi lain, anggur laut (*Caulerpa lentillifera*) kaya akan kandungan antioksidan. Penelitian ini bertujuan untuk mengetahui pengaruh *C. lentillifera* dan parasetamol terhadap kadar gula darah tikus putih (*Rattus norvegicus*) jantan. Tikus putih jantan dewasa galur Wistar berumur 3-4 bulan dengan bobot rata-rata 160 g digunakan sebagai hewan coba dalam penelitian ini. Sebanyak 25 ekor tikus putih dibagi menjadi lima kelompok perlakuan. Kelompok I diberikan perlakuan yang sama namun diganti dengan plasebo. Kelompok II-V diberikan parasetamol dengan dosis 250 mg/kg/BB setiap hari. Perlakuan anggur laut pada Kelompok III diberikan dengan dosis 10 g/kg/BB/hari, Kelompok IV diberikan dosis 15 g/kg/BB/hari, dan Kelompok V diberikan dosis 20 g/kg/BB/hari. Bahan induksi (anggur laut dan parasetamol) diberikan secara oral, kemudian kadar gula darah diukur pada hari ke-11 perlakuan menggunakan glukometer. Hasil uji sidik ragam satu arah menunjukkan bahwa anggur laut memberikan pengaruh yang signifikan terhadap kadar gula darah ($P \leq 0,01$). Hal ini membuktikan bahwa kandungan antioksidan pada anggur laut secara aktif memengaruhi perubahan kadar gula darah akibat induksi parasetamol. Uji statistika lanjutan menggunakan uji jarak berganda Duncan menunjukkan bahwa tidak terdapat perbedaan yang signifikan ($P > 0,05$) pada berbagai dosis anggur laut yang diberikan. Keberadaan flavonoid dalam anggur laut, yang merupakan salah satu senyawa katekin, dapat memberikan efek antioksidan yang sama meskipun pada dosis yang lebih rendah.

Kata-kata kunci: kadar gula darah; *Caulerpa lentillifera*; parasetamol; tikus putih

INTRODUCTION

Paracetamol is a commonly used as an analgesic and antipyretic drug that considered are very safe to use (Freo *et al.*, 2021). The use of paracetamol beyond its reasonable threshold (commonly called a toxic dose) can cause organ damage. When consumed in excess of therapeutic doses, it is known to cause hepatotoxicity but is rarely an etiologic agent of pancreatitis (He *et al.*, 2018). A single dose of paracetamol at 750 mg/kg body weight (BW) in white rats caused significant hepatocyte degeneration (Gupta *et al.*, 2023), whereas in the pancreas, a dose of 1000 mg/kg BW was required to induce damage (Aboshama *et al.*, 2024). Paracetamol overdose can cause significant morbidity and mortality (Chiew *et al.*, 2018). Paracetamol poisoning in cats presented to the Veterinary Clinic of Universitas Gadjah Mada, Yogyakarta, Indonesia, in 2020 was reported in more than 20 cases, with clinical signs including methemoglobinemia, cyanosis and hepatotoxicity (Yanuartono *et al*., 2020). Paracetamol poisoning in six dogs has also been reported at the Veterinary Clinical Complex, College of Veterinary Science and Animal Husbandry, of Kamdhenu University, Anand, India (Shah *et al*., 2024). Cases of paracetamol poisoning in dogs and cats in lay people, both intentionally and unintentionally, are one of the reasons why this drug needs attention.

Various possibilities, such as drug abuse by the owner and improper storage of drugs resulting in accidental ingestion (Bertero *et al.*, 2020). Cyanosis, anaemia, and jaundice are clinical signs of paracetamol toxicity in dog and cat which are caused by decreased detoxification saturation and the amount of glutathione (Bates 2016). It's been known that decreased glutathione levels also decrease blood sugar

levels (Lutchmansingh *et al.*, 2018).

The pancreas is the main key in the secretion of insulin and glucagon hormones which play a role in regulating blood sugar levels. Pancreatic α and β cells have a function to produce glucagon and insulin with a total percentage approaching 80% of the total cells in the islets Langerhans can be affected if there are metabolic or tissue disorders that occur in the main body of the pancreas (Röder *et al.*, 2016). The impact of metabolic disorders in the pancreas will directly affect blood sugar homeostasis due to abnormalities in tissue damage caused by oxidative metabolism by N-acetyl p-benzoquinone imine (NAPQI) from paracetamol. Conjugation of NAPQI with glutathione causes the detoxification mechanism of NAPQI (Wang *et al.*, 2017). One of the ways to overcome this disorder is to use natural ingredients such as sea grapes (*Caulerpa lentillifera*) with active antioxidant ingredients.

Caulerpa lentillifera, also known as sea grapes or green caviar is green algae that has active antioxidants (Wirawan *et al.*, 2022). In addition, sea grapes (*C. lentillifera*) contain minerals such as calcium (Ca) 2,318–2,406 mg, sodium (Na) 9,338–21,748 mg, phosphorus (P) <139.54 mg, zinc (Zn) <3.40 mg, and copper (Cu) <1.05 mg per 100 g. The Ferric Reducing Ability of Plasma (FRAP) content of *C. lentillifera* is included in the high levels, namely at 27.09 mg TE/100 g. FRAP is the antioxidant capacity in plasma. The Total Flavonoid Content (TFC) and Total Phenolic content (TPC) found in *C. lentillifera* also showed a good value, 1506.41 mg QE/100g and 57.95 mg GAE/100g respectively (Ismail *et al.*, 2020). Phenolics and flavonoids are considered powerful antioxidants and revealed to be more effective than Vitamins C, E and carotenoids. The antioxidant properties of phenolics and flavonoid compounds are demonstrated by several things, such as the destruction of radical species such as Reactive Oxygen Species/Reactive Nitrogen Species (ROS/RNS), suppressing the formation of ROS/RNS by inhibiting several enzymes or chelating trace metals involved in the production of free radicals, and regulating or protecting antioxidant defenses (Kaurinovic and Vastag, 2019).

The presence of free radicals generated by paracetamol, which can exert detrimental effects on the pancreas, may impair insulin and glucagon secretion, thereby affecting plasma glucose levels. Conversely, sea grapes possess a high antioxidant content, which is expected to neutralize the free radicals produced by paracetamol. This study was conducted to determine the effect of *C. lentillifera* on changes in blood sugar levels in male white rats due to paracetamol induction.

RESEARCH METHODS

Ethical Clearance

Experimental animals play an important role in research. The use of experimental animals must consider a balance between scientific objectives and animal welfare ethics. The experimental animals used in this study have obtained ethical approval through ethical clearance No. B/100/UN14.2.9/ PT.01.04/2024, issued by the ethics commission of the Faculty of Veterinary Medicine, Udayana University. This approval confirms that the research procedures complied with the principles of animal use and animal welfare standards.

Experimental Animals

The object of this study consisted of 25 male Wistar strain white rats (*Rattus norvegicus*) that were clinically healthy, with a body weight of 160.12 ± 13.16 g and aged 3–4 months. The sample size was determined using Federer's formula, $(t - 1)(n - 1) \geq 15$, which *t* is the number of treatments and *n* is the number of replications per treatment. With five treatments, the minimum number of replications required was five per treatment. The rats were obtained from a rat breeding facility in Denpasar City, Bali. Healthy rats were placed in cages with access to *ad libitum* food and drinking water and environmental control to minimize

stress. Prior to treatment, the rats were acclimatized for seven days.

Experimental Design

This study used a Completely Randomized Design (CRD) with 25 white rats randomly assigned to five treatment groups (Table 1). The negative control group (P0) received a placebo. The positive control group (P1) was administered paracetamol (Sanmol Forte®, PT. Sanbe Farma, Bandung, Indonesia), at a dose of 250 mg/kg BW. Treatment groups P2, P3 and P4 received paracetamol (250 mg/kg BW) combined with sea grape (*C. lentillifera*) simplicia at doses of 10, 15 and 20 g/kg BW, respectively. All treatments were administered orally by gavage for 14 days. It has already been tested that the dose of paracetamol to cause liver damage is 250 mg/kg BW (Utami *et al.*, 2017).

Table 1. Treatment dose variants

Group	Paeacetamol dose mg/kg BW	Sea grape dose mg/kg BW
I	0	0
II	250	0
III	250	10
IV	250	15
V	250	20

Blood Sugar Level Examination

Rat's blood sugar levels were measured using a glucometer (EasyTouch®, MHC Medical Products, Fairfield, Ohio, USA) with automatic results shown in mg/dL. Blood sampling was carried out through the coccygeal vein. The blood that came out of the puncture was directly dripped onto the test strip that had been inserted into the glucometer slot. The results of the blood sugar level measurement were displayed directly on the glucometer screen in units of mg/dL.

Data Analysis

Parametric data of the blood sugar level measurements were analyzed using One Way Analysis of Variance. The Duncan multiple range test were used to determined the difference in sea grapes dosage later be conducted if the One Way ANOVA results show a significant difference (Sa'diyah and Hariani, 2021).

RESULTS AND DISCUSSION

Based on this study, the One Way ANOVA test (Table 2) showed that there is a very significant difference ($P \leq 0.01$) for each treatment group. These result shows that the sea grapes increase the blood sugar level of the paracetamol induced rats. Duncan's test (Table 3) indicated no significant difference in the effect of the different doses of sea grapes given. The final results in Table 4 show the average blood sugar levels in all treatment groups.

In the experimental group, treatments group were considered as the standard blood sugar level. Group I has the highest averages of blood sugar levels which is caused by all the carbohydrates consumed through pellets which will later be converted into glucose in the liver, thus affecting blood sugar levels (Utami *et al.*, 2017). Blood sugar levels in Group II seemed to be lower by 62 mg/dL than Group I and it turned out to be the lowest blood sugar level among all treatments. This low blood sugar level is estimated to be caused by an early stage of insulin resistance deficiency mechanism. Insulin resistance is defined as a condition of weakening of the effect of insulin on glucose metabolism. The resulting hyperinsulinemia is a characteristic of insulin resistance that occurs in the early stages of the disease. Within normal physiological conditions, increased insulin concentration is an adaptive response to environmental factors. If hyper insulinemia persists for a long time, the expression of insulin receptors on the plasma membrane decreases (Unluhizarci *et al.* 2021). This is the initial mechanism of insulin resistance that can lead to hypoglycaemia. In further statistical testing to find the effect of different doses of sea grapes on blood sugar levels, all treatments obtained a *p-value* stating that

Table 2. One way Analysis of variance report on blood sugar level result

	Sum of square	Df	Mean square	F	Sig.
Between Groups	5119.200	4	1279.800	6.806	0.001
Within Groups	3760.800	20	188.040		
Total	8880.000	24			

Table 3. Duncan multiple range test report on blood sugar level result

Group	N	1	2
2	5	107.60	
3	5	112.40	
5	5	116.60	
4	5	126.40	
1	5		148.00
Sig.		0.059	1.000

Table 4. Average blood sugar level in male white rats after treatment

Group*	Blood sugar level (mg/dl)
I	162
II	100
III	118
IV	134
V	121

Note: Group I = placebo; Group II = paracetamol 250 mg/kg BW; Group III = paracetamol 250 mg/kg BW and sea grapes 10 g/kg BW; Group IV = paracetamol 250 mg/kg BW and sea grapes 15 g/kg BW; Group V = paracetamol 250 mg/kg BW and sea grapes 20 g/kg BW.

there was no significant difference (P>0.05). Flavonoids content in sea grapes act as α-glucosidase enzyme inhibitor (Zhu *et al.,* 2020). Flavonoids will inhibit the mechanism of the α-glucosidase enzyme which functions to absorb carbohydrates and then break them down into monosaccharides so that blood sugar levels decrease (Yasaroh *et al.,* 2021). The content of sea grapes is also known to increase lipid accumulation and glucose absorption through glucose transpoter 4 (GLUT-4) expressions so sea grapes not only work to increase insulin secretion but also glucose absorption (Sharma *et al.,* 2017).

In Groups III, IV and V, the average blood sugar levels were not significant. Group III experienced a decrease of 44 mg/dL than Group I. Similarly, Group IV also had a blood sugar level decrease that was not significant compared to other groups, namely 28 mg/dL lower than Group I. Subsequently, treatment group V had a difference in blood sugar levels of up to 41 mg/dL lower than Group I. The sea grapes (*C. lentillifera*) has minerals contain such as calcium (Ca) 2,318–2,406 mg, sodium (Na) 9,338–21,748 mg, phosphorus (P) <139.54 mg, zinc (Zn) <3.40 mg, and copper (Cu) <1.05 mg per 100 g. The sea grapes also has antioxidant contain such as Ferric Reducing Ability of Plasma (FRAP) 27.09 mg TE/100 g, Total Flavonoid Content (TFC) 1506.41 mg QE/100g and Total Phenolic content (TPC) 57.95 mg GAE/100g (Ismail *et al.,* 2020). This condition may be caused by the correlation of catechin content in sea grapes. Catechin is a compound derived from polyphenols with high antioxidant content (Anjarsari and Ratna, 2016). One of the catechin compounds found in sea grapes is flavornoids. It is known that catechin content can cause a synergistic effect that makes the same antioxidant effect that can be achieved at a lower dose (Machin *et al.,* 2021).

CONCLUSION

Administration of *C. lentillifera* at doses of 10, 15 and 20 g/kg BW is proven to affect changes in blood sugar levels due to paracetamol induction in male white rat.

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SUGGESTION

Further research is needed to determine exact mechanism by which antioxidant can influence blood glucose level in White rats administered paracetamol and sea grapes (*C. lentillifera*).

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