Food Research 8 (5) : 1 - 7 (October 2024)
Journal homepage: https://www.myfoodresearch.com

FOOD RESEARCH

RESEARCH PAPER

The effect of sea grapes (*Caulerpa racemosa*) powder drink on improvement of obesity biomarker in Wistar rats

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Article history:
Received: 21 October 2022
Received in revised form: 22 November 2022
Accepted: 6 December 2022
Available Online: 2 September 2024

Keywords:
Cholesterol,
Drink,
Lee's index,
Sea grapes,
Wistar rat

DOI:
https://doi.org/10.26656/fr.2017.8(5).478

Abstract

Obesity has become a global public health issue due to its rapidly increasing prevalence. Sea grapes powder drink (SPD) as a functional food has the potential to become an important biomarker in the improvement of obesity. The biomarkers in obesity can be assessed by Lee's index and lipid profile. Due to its high antioxidant content, SPD can improve both Lee's index and lipid profile. The objective of this study was to analyse the effect of SPD on the obesity biomarkers of Wistar rats. In this research, a completely randomized design that involved 24 male rats weighing between 150–250 g was used. Rats were randomly put into six groups. Biomarkers were measured using Lee's index, lipid profile and the weight ratio of both visceral fat and liver. Results after 21 days of intervention showed a reduction in Lee's index in the group that was given HFD + SPD 1 g, 1.5 g and 2 g. The visceral fat weight ratio in HFD + SPD 1.5 g and 2 g group significantly decreased. However, it had no effect on the liver weight ratio. Levels of Total Cholesterol (TC), Triglyceride (TG), and Cholesterol-Low Density Lipoprotein (C-LDL) in the HFD + SPD 1 g, 1.5 g and 2 g group significantly decreased. The Cholesterol -High Density Lipoprotein (C-HDL) dramatically increased HFD + SPD 2 g group. SPD is effective in improving Lee's index, visceral fat weight ratio and lipid profile but not liver weight ratio. SPD can be used as an alternative therapeutic product in the management of obesity and consequent reduction of its prevalence.

1. Introduction

The exponential growth of obesity has become a worldwide public health issue (Khutami *et al*., 2022). The global prevalence of obesity is predicted to increase from 15% (764 million) in 2020 to 18% (1,025 million) in 2030 (Federation, 2022). The prevalence of obesity is growing in developed, middle-income, and low-income nations (Endalifer and Diress, 2020). Indonesia is the fourth most populated nation in ASEAN, with a 6.9% obesity rate (WHO, 2016). According to the National Health Research (RISKESDAS) statistics report, the prevalence of obesity increased by 11.8% between 2007 and 2018 (Kemenkes, 2018).

Obesity is an excessive buildup of fat that leads to metabolic syndrome disorders such as diabetes mellitus, cardiovascular disease, hyperlipidemia and Non-Alcoholic Fatty Liver Disease/NAFLD (Klop *et al*., 2013). Consumption of excessive amounts of high-energy meals and inadequate physical exercise are the main causes of obesity (Hruby *et al*., 2016; Lakerveld and Mackenbach, 2017). The regulation of diet and increase in physical activity is necessary for obesity management (Kemenkes, 2015). Obesity management based on a diet requires careful consideration of fiber and vitamin consumption (Damasceno *et al*., 2013).

Seaweed treatment is considered to be an anti-obesity drug in the creation of functional food diversification because it contains phytonutrients including carotenoids, phenols, and alginates (Wan-Loy and Siew-Moi, 2016). One of the well-known species of

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eISSN: 2550-2166
Published by Rynnye Lyan Resources

seaweed is Sea grapes (*Caulerpa racemosa*), which is a green macro-alga that appears as small circular-like fish eggs and is sometimes referred to as green caviar (Sherly and Asnani, 2016; Pereira, 2018). Communities in the Indo-Pacific area have a history of consuming sea grapes, which are farmed in ponds, particularly in Indonesia (Gaillande *et al*., 2017). Sea grapes are a source of antioxidants that can reduce adipogenesis and lipid profile (Matanjun dan Muhammad 2010; Preez *et al.,* 2020). Research shows that *Caulerpa racemosa* has better antioxidant content than *Caulerpa lentilifera* (Yap *et al.*, 2019). Sea grapes are a readily accessible, inexpensive and easily accessible native cuisine that can be eaten immediately. They also have a distinct aroma of fresh seaweed (Battu *et al*., 2019; Ojulari *et al*., 2020). Due to their high water content, sea grapes must first be dried to make them simple to store and preserve in order to increase their value (Wibowo and Fitriyani, 2012; Permata and Sayuti, 2016).

Previous preclinical studies reported that ingesting 1.5 g of sea grapes (*Caulerpa lentilifera*) for 16 weeks decreased total cholesterol, triacylglycerol, and C-HDL by 18.5%, 37.7%, and 48.2%, respectively (Matanjun and Muhammad, 2010). Another research showed the impact of *Caulerpa lentilifera* on Lee's index and visceral fat of rats (Preez *et al.,* 2020). The research involved ingestion of doses of up to 1.3 g of powder per day for eight weeks resulting in weight reduction of rats. Publicly available studies on the effects of sea grapes (*Caulerpa racemosa*) on Lee's index and lipid profile in obese rats are currently limited. Therefore, this study aimed to analyze the effect SPD has on biomarkers of obesity (Lee's index, weight ratio of visceral fat and liver as well as lipid profile) in obese Wistar rats.

2. Materials and methods

2.1 Intervention product

The sea grapes (*Caulerpa racemosa*) were obtained from the district of Takalar in the province of South Sulawesi in Indonesia. In the preparation of SPD, 1 kg of sea grapes was washed, blended and mixed with various ingredients (arabic gum, sucralosa, tastagem powder and essence). The resulting mixture was then dried. The procedure for laboratory preparation of sea grapes powder involved using a vacuum evaporator at 4°C for approximately 1 hr (Christiana *et al.,* 2015; Nurwanto and Suswantinah, 2021).

2.2 Nutritional evaluation

The Standard Association of Official Analytical Chemistry method was conducted to determine the percentage composition of carbohydrate (by-difference method, AOAC 2005-991.43), protein (Kjeldahl method, AOAC 2006-991.20), fat (Soxhlet method, AOAC 2006-991.20), beta-carotene (HPLC method, AOAC 2005-938.04), soluble and insoluble fiber (gravimetric method, AOAC 2005-991.43) as well as ash content was determined using gravimetric method (SNI 1992-01.2891) (Badan Standardisasi Nasional, 1992; AOAC, 2005; AOAC, 2006).

2.3 Experimental animals

This study was experimental and involved the use of a completely randomized design. Male Wistar rats (*Rattus novergicus*) ranging between 2-2.5 months of age with weights of 150-250 g were used. The rats were obtained from Biomedical Technology Indonesia. The Federer 1966 formula was utilized to determine the sample size of rats. As a result, 24 male rats were considered. The rats were acclimated to a room with a 12 -hour cycle of light and dark for 14 days. For 60 days, rats were fed with a high-fat diet (46% fat) (Matias *et al.,* 2015), and then administered with SPD for 21 days. In the last treatment, the rats were anesthetized with a mixture of 80 mg of ketamine and 5 mg of xylazine per kilogram of body weight. The liver and visceral fat were collected and analyzed. Paramedics at the Bogor Agricultural University biopharmaceutical laboratory collected blood serum samples from the rats to examine lipid profiles. The research obtained permission from the Animal Ethics Commission, Faculty of Veterinary Medicine, Bogor Agricultural University with approval number 015/KEH/SKE/VI/2021.

2.4 Animal diet

Rats were provided with unlimited food and water. During acclimatization, all rats were fed the same diet. All groups were provided with a high-fat diet for 60 days until Lee's index value reached or exceeded 300 with the exception of the normal feeding group. The diet was maintained throughout the duration of the trial. The baseline blood samples and body measurements of the rats were taken. Standard Diet (SD), High Fat Diet (HFD), HFD + Orlistat, HFD + SPD 1 g, HFD + SPD 1.5 g, and HFD + SPD 2 g were the six dietary treatments administered to Wistar rats. Orlistat and SPD were initially dissolved in 3 mL of carboxymethyl celulose (CMC) and administered orally for 21 days.

2.5 Chemical and tools

The tools used for lipid profile analysis consisted of a biochemical analyzer, biomaxima and glory diagnostic kits. Weight scales and measuring tapes were used to measure Lee's index. Scissors, syringes, probes and scalpels were used in surgery. Anesthetization of rats was done using 80 mg of ketamine and 5 mg of xylazine. CMC of 0.5% concentration was used to dissolve sea

https://doi.org/10.26656/fr.2017.8(5).478

grapes powder and orlistat.

2.6 Research parameter

Data on body weight and body length was collected using a digital scale and measuring tape respectively. Obesity biomarkers were analyzed using Lee's index. The formula for Lee's index used was 1/3 (weight) × (length) - 1000 (Suleiman *et al*., 2022). The ratios of visceral fat weight to body weight as well as liver weight to body weight were measured. Serum samples were analyzed to ascertain the levels of TC, TG, and C-HDL. This process was done using the Incubio brand biochemical analyzer twice before and after the administration of SPD. C-LDL was computed concurrently using the Anandita formula (C-LDL = 0.9 × Total Cholesterol – (0.9 × Triacylglycerol)/5-28) (Krishnaveni and Gowda, 2015).

2.7 Statistical analysis

The data was statistically evaluated using Excel and SPSS Version 22 and reported as mean standard error. The differences between groups were statistically examined using ANOVA followed by Duncan's test. Data was analyzed and considered statistically significant at $p<0.05$.

3. Results

Table 1 shows the chemical content of sea grapes powder drink with carbohydrates representing the highest content and fat the lowest. In addition, SPD also contains 48.21±0.80 mg/kg of beta-carotene as an antioxidant.

Table 1. Chemical content of sea grapes powder drink.

Component	Total
Carbohydrate (%)	77.59±0.50
Protein (%)	4.06±0.35
Fat (%)	0.52±0.20
Ash (%)	5.32±0.65
Insoluble Fiber (%)	1.87±0.07
Soluble Fiber (%)	13.97±0.12
Beta carotene (mg/kg)	48.21±0.80

ANOVA test showed that the Lee's Index was not different among groups before SPD administration, as shown in Table 2 ($p = 0.394$). After 21 days of intervention, rats that were fed with HFD + SPD 1 g, 1.5 g and 2 g groups had significantly decreased Lee's index scores compared to rats in the HFD + orlistat group (p-value = 0.001). The visceral fat weight ratios of the HFD + SPD 1.5 g and 2 g groups were significantly lower than those of the HFD + orlistat group ($p = 0.030$). However, there was no significant change in the liver weight ratio.

After 21 days, there was a decrease in TC, TG, and C-LDL among the HFD + SPD 1 g, 1.5 g and 2 g groups as shown in Table 3. The ANOVA test results showed a significant difference in the lipid profile reduction of HFD + SPD 1 g, 1.5 g and 2 g groups in comparison with the HFD groups (p-value = 0.009, 0.035, 0.009). The C-HDL levels in the HFD + SPD 2 g group increased ($p = 0.046$). The results of this research indicated that SPD was effective in improving lipid profile.

4. Discussion

The effect on Lee's index is more prominent in the HFD + SPD groups compared to the HFD + Orlistat group. The higher the dose in treatment, the greater the reduction in Lee's index and visceral fat ratio of rats. The results of this study are consistent with previous studies which showed that 10 weeks' supplementation of sea grapes extract reduced body weight in obese mice (Sharma *et al*., 2017). This reduction in weight was due to the action of beta-carotene and fiber contained in SPD. The beta-carotene content of SPD was 48.21±0.8 mg/kg and was considerably higher than that of grapes beverage (0.39 mg/kg) (Elejalde *et al*., 2021). Previous studies have also shown that carotene can act as a chemical regulator of adipocytes and fat storage (Mounien *et al*., 2019). The effect of carotene and its derivatives has been

Table 2. Effect of sea grapes powder drink on Lee's index, visceral fat ratio and liver ratio.

Group	Lee's Index 0 Day	Lee's Index 21 Day	Δ Lee's Index	Visceral Fat Weight Ratio (g)	Liver Weight Ratio (g)
SD	298.94±6.18^{a}	297.88±8.54^{ab}	-1.06±3.40^{a}	0.81±0.13^{a}	2.90±0.82
HFD	311.34±1.37^{a}	317.29±4.54^{bc}	5.95±4.55^{a}	2.59±0.33^{b}	3.32±0.18
HFD + Orlistat	308.15±4.29^{a}	307.04±6.15^{c}	-1.12±5.35^{a}	2.06±0.45^{b}	3.09±0.34
HFD + SPD 1 g	307.53±6.07^{a}	291.49±3.33^{a}	-16.04±3.83^{b}	2.28±0.37^{b}	3.08±0.49
HFD + SPD 1.5 g	301.61±1.60^{a}	286.46±4.29^{a}	-15.15±3.67^{b}	1.67±0.37^{a}	3.31±0.30
HFD + SPD 2 g	306.82±4.03^{a}	286.18±1.53^{a}	-20.64±3.97^{b}	1.87±0.29^{a}	3.25±0.06
P Value	0.394	0.003	0.001*	0.030*	0.697

Values are presented as mean±SD. Values with different superscripts within the same column are statistically significantly different ($P<0.05$).

https://doi.org/10.26656/fr.2017.8(5).478

Table 3. Effect of sea grapes powder drink on lipid profile.

Group	0 Day (mg/dL)	21 Day (mg/dL)	Δ Profil lipid	p-Value
Total Cholesterol				
SD	56.26±5.74	68.50±10.33	12.23±15.51[a]	0.009*
HFD	65.96±12.91	216.18±75.09	150.22±75.49[b]	
HFD + Orlistat	71.05±4.20	41.45±4.17	29.59±4.52[a]	
HFD + SPD 1 g	92.32±29.26	69.07±16.20	-23.24±26.43[a]	
HFD + SPD 1.5 g	75.46±7.93	49.82±5.14	-25.63±5.26[a]	
HFD + SPD 2 g	75.57±4.80	49.25±7.63	-25.32±10.14[a]	
Triglyceride				
SD	43.92±2.46	43.33±4.15	-0.58±6.05[a]	0.032*
HFD	59.58±17.01	378.20±181.91	318.63±185.47[b]	
HFD + Orlistat	95.00±43.69	68.50±14.60	-26.50±36.50[a]	
HFD + SPD 1 g	84.62±20.43	80.75±20.24	-3.87±9.39[a]	
HFD + SPD 1.5 g	87.48±26.92	44.02±5.96	-43.46±21.80[a]	
HFD + SPD 2 g	147.75±78.01	101.35±37.85	-46.22±40.67[a]	
C-LDL				
SD	14.73±5.43	25.85±9.67	11.11±14.48[b]	0.009*
HFD	20.64±11.19	98.48±37.08	77.84±35.44[b]	
HFD + Orlistat	18.84±11.07	-3.01±5.53	-21.86±7.07[a]	
HFD + SPD 1 g	44.58±26.13	20.36±16.03	-24.21±22.78[a]	
HFD + SPD 1.5 g	24.16±7.99	8.91±4.76	-15.24±3.98[a]	
HFD + SPD 2 g	12.55±10.77	-1.91±10.79	-14.47±9.27[a]	
C-HDL				
SD	61.10±4.70	83.29±9.51	22.18±5.03[a]	0.046*
HFD	70.85±18.38	56.94±10.71	-13.90±19.51[a]	
HFD + Orlistat	36.45±4.78	92.50±25.82	56.79±22.55[a]	
HFD + SPD 1 g	25.28±3.38	84.76±17.53	59.48±18.55[a]	
HFD + SPD 1.5 g	71.32±19.46	136.88±46.93	65.56±39.49[a]	
HFD + SPD 2 g	43.48±3.74	136.88±46.93	127.22±43.34[b]	

Values are presented as mean±SD. Values with different superscripts within the same column are statistically significantly different (P<0.05).

documented in adipogenesis as an aid in obesity management through inhibited proliferation and differentiation (Bonet *et al*., 2015). β-Carotene inhibits adipogenesis through the production of β-apo-14′-carotenal and repression of Peroxisome Proliferator Activator Receptor Gamma (PPARγ) as well as Retinoid X Receptors (RXR) activation (Ziouzenkova *et al*., 2007). Furthermore, carotene and its derivatives inhibit adipogenesis by suppressing the signaling of the Alfa Threonine Protein Kinase (AKT) cascade which is a signal transducer of the insulin pathway. Carotene has also been shown to suppress PPAR gamma and Sterol Regulatory-Element Binding Protein1 C (SREBP1-C) in the early phase of adipose tissue differentiation (Gopal *et al.,* 2021; Mumu *et al.,* 2022).

The results of this study showed no significant difference in liver weight ratio between the treatment groups. This was due to the short intervention duration. However, results from another study where the *Caulerpa lentilifera* intervention was 112 days long showed a significant reduction in liver weight (Preez *et al.* 2020).

In addition to reducing adipogenesis, SPD can also improve lipid profile in obese rats. The results of this study showed that giving SPD at a dose of 2 g for 21 days could reduce TC, TG, C-LDL and increase C-HDL in obese rats previously fed a high fat diet with 46% fat for 60 days. These results are in line with previous studies which demonstrated that supplementation of *Caulerpa* sp. could improve lipid profile in 112 days (Preez *et al.,* 2020). In contrast, administration of 0.8 g of sea grapes powder for 14 days in hypercholesterolemic rats who had previously received a high-fat diet with 11% fat for 21 days could not increase the C-HDL (Dewi *et al*., 2014). This is due to the shorter duration of the intervention and the use of a low dose. Beta-carotene can decrease profile lipid through

https://doi.org/10.26656/fr.2017.8(5).478

decreased expression of genes that control lipogenesis namely SREBP1-C, Fatty Acid Synthesis (FAS), and Acetyl CoA Carboxylase (ACC) as well as increased expression of genes that control lipolysis such as Acyl CoA Oxidase 1 (ACOX1), Carnitine Palmitoyl Transferase1 (CPT1), Adipose Triglyceride Lipase (ATGL) and Hormone Sensitive Lipase (HSL) (Lobo *et al.,* 2010; Gómez-Zorita *et al.,* 2020; Mumu *et al.*, 2022)

The water-soluble fiber content of SPD was 13.97%. This is higher than the 11.83% water soluble fiber content found in *Eucheuma cottoni* powder drink (Wibowo dan Fitriyani, 2012). Water-soluble dietary fiber is known to lower plasma cholesterol levels. Sea grapes contain water-soluble fiber in form of alginate, sulfate and inulin that significantly reduce plasma cholesterol levels. The dietary fiber (alginate gel matrix) traps fatty acids forming a gel thereby agglomerating the feces (Matanjun and Muhammad, 2010). This study, therefore, showed that the fiber and beta-carotene from SPD could improve lipid profile as observed in a previous study where beta-carotene and fiber from sweet potatoes and pumpkin inhibited SREBP-1C in the liver of hypertriglyceridemic rats (Sunarti *et al*., 2022).

SPD has low-fat content and can therefore be consumed by obese individuals (Tapotubun *et al*., 2020). Polyunsaturated fatty acids (PUFA) are one of the types of fat found in sea grapes (Magdugo *et al*., 2020). The PUFA content of sea grapes is as high as 38.07% (Nagappan and Vairappan, 2014). Sea grapes have a high PUFA/SFA (Saturated Fatty Acids) ratio of 0.52 in addition to a low atherogenic and thrombogenic index (TI). Consequently, they can provide excellent protection against coronary artery disease (Magdugo *et al*., 2020). A previous study showed that PUFA also improved lipid profile through inhibition of Hormone Sensitive Lipase (Zuliani *et al*., 2009).

The impact of this study is seen in availing SPD as an alternative therapeutic product in the management of obesity. This research has several limitations consisting of a short intervention period that was not enough to observe the effect of SPD on liver weight ratio. Furthermore, the research mainly focused on one type of *Caulerpa* sp. Lastly, other factors that may affect obesity biomarkers such as glucose levels were not analyzed.

4. Conclusion

Sea grapes powder drink can improve obesity biomarkers like Lee's index, visceral fat-to-weight ratio and lipid profile. However, there was no observable effect of SPD on the liver weight ratio. Future research should focus on studying the effect of SPD on obesity biomarkers for longer periods as well as trials in other animals such as monkeys. In addition, it is recommended to conduct studies involving comparisons of the effects of different types of sea grapes on obesity. Other types of sea grapes include *Caulerpa lentilifera, Caulerpa taxifolia* and *Caulerpa okumura.*

Conflict of interest

There are no conflicts of interest among the authors of this work. This study is part of the author's dissertation.

Acknowledgments

The authors would like to appreciate the support Saraswanti Indo Genetech laboratory offered in assessing the SPD product. Special thanks to the Tropical Biopharmaca Research Centre Bogor Agricultural University, as well as the paramedics who made it possible to utilize the facilities and infrastructure. Great appreciation also goes to those who assisted with the care of experimental animals.

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