SUCROSE HSD

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Effect of *Chlorella vulgaris* Extract on High Sucrose Diet-Induced Diabetes in *Drosophila melanogaster*

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ABSTRACT. Microalgae *Chlorella vulgaris* is a microscopic green algae which has known potential as a source of food and medicine (functional food). However, the pharmacological capacity of this microalgae species against disease due to metabolic disorders is still not understood. Thus, this study aims to evaluate the effect of *C. vulgaris* extract on animal models of *Drosophila melanogaster* (*Drosophila*) which are fed high-sucrose diet (HSD). Wild type *Drosophila* was used in this study for 7 days of observation. *Drosophila* was divided into four groups consisting of the first group that was not treated as a control. The second group was treated with HSD (30%), the third group was treated with *C. vulgaris* extract (120 g/L) and the fourth group was treated double treatment (HSD and *C. vulgaris* extract). The parameters observed included fecundity, hatchability, hemolymph glucose and triglyceride levels. The results showed that the extract of *C. vulgaris* was able to reduce the negative effects of giving HSD. The single treatment of *C. vulgaris* extract and double treatment between *C. vulgaris* extract and HSD significantly decreased levels of hemolymph glucose, triglycerides of *Drosophila,* while the parameters of fecundity and hatchability were significantly increased when compared to *Drosophila* which only received HSD treatment. The conclusion of this study is that *C. vulgaris* extract can be used as an antihyperglycemic agent which requires further study to prove the results that have been obtained.

Key words : Chorella vulgaris, diabetes, Drosophila, sucrose

PENDAHULUAN

Currently, people often consume foods and drinks that contain high sugar levels. Even though high sugar intake is the main cause of the emergence of various deadly diseases (Bai *et al*. 2018). In the body, sugar will be digested, absorbed and converted into monomer compounds, namely monosaccharides. Furthermore, these simple sugars are transported by the blood to cells and tissues to be metabolized (de Aquino Silva *et al*., 2020). Consumption of foods with high sugar levels in the long term will disrupt the homeostasis of glucose

metabolism in the body. Metabolic disorders in the body can be in the form of hypertension, coronary heart disease, stroke, cancer and most importantly type 2 diabetes mellitus (T2DM) (Harshavardhana & Krishna, 2019).

As a disease with metabolic disorders, T2DM has distinctive symptoms, including high blood glucose and triglyceride levels (Musselman *et al*., 2019). If the development of this disease cannot be controlled, it will result in the emergence of various serious problems such as blindness, kidney failure, amputation and permanent disability (Rani *et al*., 2020). Actually, new cases of the disease are increasing with characterized by its immergence in children which previously was only found in adults. The treatment of T2DM uses insulin as a synthetic hypoglycemic agent which is given either orally or by injection (Priyadarsini *et al*., 2020). This treatment is very risky with more severe side effects such as damage to the eyes, kidneys, heart and others (Oyeniran *et al*., 2020).

Microalgae have long been known for various degenerative disease therapies. *C. vulgaris* is a microscopic green algae that is used as a supplement and functional food (Gui *et al*., 2019). The content of phenolic compounds from this species of microalgae strengthens its function as a source of antioxidant compounds that can improve metabolism that occurs in the human body (Tugcu *et al*., 2017). The antioxidant ability of *C.vulgaris* extract is high enough that it can stabilize free radicals that will damage DNA, mitochondria and other organelles (Zakaria *et al*., 2017). However, the regulation of *C. vulgaris* against metabolic disorders due to consuming high sugar levels is not clearly understood.

Drosophila or fruit flies have long been known as animal models that can be used to study diabetes. This is because fruit flies have 74% homologous genes with human genes that control various diseases including diabetes mellitus (Westfall *et al*. 2018). In addition, the mechanism of glucose homeostasis can be fully observed through these fruit flies. Based on the observations of Wang *et al*. (2020), *Drosophila* can show characteristics of T2DM patients such as symptoms of hyperglycemia.

Thus, in this study, the effect of extracts from microalgae *C. vulgaris* was observed on the appearance of symptoms of T2DM in animal models of HSD-induced *Drosophila*. The observations conducted in the study will be presented in this article which includes fecundity, hatchability, hemolymph glucose and triglyceride levels. Meanwhile, *C. vulgaris*

extracts were observed for total phenolic level and antioxidant activities using the *Diphenyl Picryl Hydrazyl* (DPPH) method. The results of this study serve as the basis for preclinical drug discovery using *C. vulgaris* microalgae.

MATERIALS & METHODS

Culture and Treatment of *Drosophila*

Drosophila used is the wild type obtained from the collection of Plant Physiology Laboratory, Department of Biology, UIN SGD Bandung. *Drosophila* was reared in a culture vial containing 10 ml of solid medium with the following composition: 1% weight /volume (w/v) of yeast; 2% w/v sucrose; 1% w/v powdered milk; 1% w/v agar and 0.08% w/v nipagine (Brookheart *et al*., 2017). The treatment was started from *Drosophila* in the 3rd instar phase and the observations were carried out for 7 days of treatment. Four of treatment groups were prepared, namely the first group *Drosophila* that was not treated as a control. The second group *Drosophila* that received 30% of HSD treatment, the third group *Drosophila* that received treatment 120 g of *C. vulgaris* extract in 1 L medium and the fourth group *Drosophila* that received double treatment HSD and *C. vulgaris* extract. The environmental conditions around the *Drosophila* culture site were temperature of 26 ± 1 °C, relative humidity of 60 ± 5%, light intensity of 2000 lux and photoperiod of 12 h of light and 12 h of darkness.

Extraction of *C. vulgaris*

5 grams of dry biomass from *C. vulgaris* was dissolved in 25 ml of methanol p.a and stored for about 24 hours at room temperature. Then the solution was centrifuged at 4000 rpm for 15 minutes. The obtained supernatant is concentrated using a rotary epavorator at a temperature of 40-50 °C to form a concentrated extract (Chen *et al*., 2018).

Measurement of Total Phenolic Levels

Measurement of total phenolic levels in the extract of *C. vulgaris* using the procedure from McCann *et al*. (2007). with minor modifications. The extract of *C. vulgaris* was added with 35 μL of Folin Ciocalteu 1 N reagent. After leaving for 3 minutes, the solution was added

with 70 ml of 15% Na_2CO_3 solution and 284 μL of aquadest. The mixture is stored in a dark room for 2 hours. Then the OD mixture was measured on a UV-vis spectrophotometer with a wavelength of 760 nm. Gallic acid is used as a standard with a concentration range of 10 - 300 μg / mL. Meanwhile, the obtained data were expressed as mg gallic acid equivalents (GAE) per 100 g of extract.

DPPH (*Diphenyl-picrylhydrazyl*) test

The test for the antioxidant activity of *C. vulgaris* extract was carried out according to the procedure of Stockum et al. (2019). The stable DPPH solution has a purple color, but will immediately change to a light yellow color when it reacts with antioxidant compounds derived from *C. vulgaris* extract. Mixed 500 µL of *C. vulgaris* extract with 250 µL of 0.3 mM DPPH solution. The mixture is shaken until homogeneous and stored in a dark room for 30 minutes. Furthermore, the OD resistance of *C. vulgaris* extract against DPPH free radicals was measured by a spectrophotometer at a wavelength of 520 nm. The calculation of inhibition uses the following equation:

$$\left(\begin{matrix}\text{Inhibition radical} \\ \text{scavenging (\%)}\end{matrix}\right) = \frac{\text{Control Absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

Fecundity and Hatchability Test

20 female *Drosophila* aged 3 days from each group were placed in a culture vial containing a standard medium and yeast as the only food source. The drosophila was transferred every 3 hours to a completely new culture bottle containing standard medium and yeast. Calculation of the fecundity of the total eggs produced by 20 *Drosophila* per hour. After 22 hours all culture bottles were examined again and the 1st instar larvae were counted. Hatching rate is calculated from the total number of larvae divided by the total number of eggs produced (Gáliková *et al*., 2017)

Measurement of hemolymph glucose levels

This test used 35 individuals (one each for male and female *Drosophila*) for each group after seven days of treatment. A total of 2 μL of colorless hemolymph was placed on a 96-well microplate (Thermo-Scientific) which already contained 0.1% N-phenylthiourea in 50 μL of PBS (Phosphate-Buffered Saline). Furthermore, 150 μL of Glucose Autokit (Wako) reagent was added to each well, and incubated at room temperature for 20 minutes before measuring the absorbance at a wavelength of 505 nm. Calculation of glucose concentrations compared using standard curves (Navrotskaya *et al*., 2016)

Measurement of hemolymph triglyceride levels

35 male and female *Drosophila* from each treatment group were crushed to obtain their homogenate. The initial stage, homogenate in PBS was mixed with Tween 0.1%. Then the mixture was heated to 65 °C for 5 minutes so that the lipase was inactive. After the mixture cools down, vortex and add the Triglyceride infinity test reagent (ThermoFisher TR22421). Then the mixture was incubated at 37 ° C for 5 minutes. The absorbance of the mixture was measured on a spectrophotometer with a wavelength of 540 nm and the results were compared against a standard curve (Ecker *et al*., 2017)

Data analysis

The obtained data were analyzed statistically using one-way analysis of variance (Anova). If the test shows a significant difference at the 95% confidence level, then it is further tested using Duncan's Multiple Range Test. All data are presented as mean ± standard deviation. Different letter labels on each accompanying data showed significant differences in the 95% confidence interval ($P < 0.05$).

RESULTS AND DISCUSSION

Drosophila as a model animal that is often used for research on metabolic diseases such as diabetes because of its advantages, such as short life cycle, easy to manipulate of food treatment and well-known methodology of metabolic observation. Consumption of HSD stimulates disharmony of metabolic homeostasis, triggering uncontrolled inflammation that damages organelles associated with T2DM. The research is aimed at an understanding

of carbohydrate metabolism in *Drosophila* because carbohydrates are the main component of natural diets of *Drosophila*. Moreover the present study shows for the first time that *C. vulgaris* extract has a protective effect against HSD-induced diabetes symptoms in *Drosophila* by preventing oxidative stress and restoring its endogenous antioxidant defenses. The effect of *C. vulgaris* extract includes increased satiety from *Drosophila* due to the intake of organic compounds. Report from the study of Bortolatto *et al*. (2015) giving organic compounds to the diet provided *Drosophila* increased the satiety process. Furthermore, it is thought that the extract of *C. vulgaris* may act by regulating appetite in the hunger center or by certain mechanisms that correlate with food entry pathways in *Drosophila*. There is strong evidence that the inductors causing hyperglycemia have induced oxidative stress, followed by the auto-oxidation process of glucose which triggers oxidative damage.

Previous studies have shown that antioxidant compounds such as phenolic acid have the potential to delay and prevent complications associated with diabetes. Likewise, Lobo *et al*., (2010) showed that antioxidant compounds as phytochemical substances can reduce oxidative damage by free radicals. Oxidative stress can damage vital organs and compounds such as lipids, proteins, DNA and cell membranes (Therond *et al*., 2006). The potential of *C. vulgaris* extract includes inhibiting glucose absorption in *Drosophila's* body followed the use of existing glucose by increasing the activity of enzymes involved in glucose metabolism. Consumption of HSD is correlated with the development of a hyperglycemic state in *Drosophila* which is responsible for the increased oxidative stress (Ecker *et al*., 2017). Extract of *C. vulgaris* has been shown to be a compound with highly relevant functions in the antioxidant defense system. There is a correlation between hyperglycemia and oxidative stress in *Drosophila* through the emergence of an imbalance between free radical production and endogenous antioxidant physiological mechanisms (Robson et al., 2018). The results of this study demonstrate the defensive role of antioxidant compounds in the extract of *C. vulgaris* against the adverse effects of oxidative stress on *Drosophil*a.

Tabel 1. The analysis results of biomarker of HSD-induced Diabetes in *Drosophila*

Paramaters	Sex	Treatments				ANOVA
		C	S	V	S+V	
Fecundity (number/h)	♀	40.60 ± 1.20 (c)	9.60 ± 0,80 (a)	41.60 ± 1.02 (c)	25.40 ± 0.49 (b)	$p < 0.05$
Hatchability (%)	♀	98.60 ± 0.80 (b)	78.20 ± 0.75 (a)	96.40 ± 1.02 (b)	87.80 ± 1.17 (b)	$p < 0.05$
Hemolymph glucose (mg/dL)	♂	22.48 ± 0.32 (a)	77.44 ± 0.34 (c)	26.52 ± 0.43 (a)	50.72 ± 0.79 (b)	$p < 0.05$
	♀	24.18 ± 0.53 (a)	88.06 ± 0.40 (c)	26.02 ± 0.70 (a)	55.22 ± 0.54 (b)	$p < 0.05$
Hemolymph triglyceride (μg/mg)	♂	42.78 ± 0,68 (a)	86.34 ± 0.83 (c)	56.34 ± 0.56 (b)	76.48 ± 0.85 (c)	$p < 0.05$
	♀	45.9 ± 0.55 (a)	96.56 ± 0.45 (c)	62.88 ± 0.74 (b)	81.16 ± 0.57 (c)	$p < 0.05$

Note: C = Control, S = HSD, V = *C. vulgaris* extract and S + V = HSD + *C.vulgaris* extract, ♂ = male, ♀ = female. The different alphabets for each data value shows significantly different at DMRT test with $\acute{\alpha} = 0.05$)

The DMRT results showed that the Drosophila group that received *C. vulgaris* extract treatment produced the number of eggs that was not significantly different from the number of eggs from the control *Drosophila* group. Likewise, the number of eggs that hatched in the *Drosophila* group treated with *C. vulgaris* extract was the same as the *Drosophila* control group, but it was also not significantly different from the *Drosophila* group that was given double treatment with *C. vulgaris* extract and HSD (Table 1). Moreover, *Drosophila* has the ovary as the largest organ of the other organs. Observation of this organ has been carried out for a long time and various treatments can affect reproductive ability including the number of eggs produced (Diop *et al.,* 2015) It is acceptable to use female *Drosophila* affected by HSD treatment because of the positive correlation between ovarian size and the number of eggs produced (Mendes and Mirth, 2016). Disorders of the reproductive organs of Drosophila due to HSD treatment can be seen from decreased egg production and fertility and the accumulation of triglycerides (Buescher *et al.,* 2013). The data from this study correlate with

research by Werthebach *et al*. (2019) showing that HSD treatment of *Drosophila* will decrease egg production. However, oxidative stress can be caused by the entry of dietary components such as carbohydrates, which continues with changes in metabolite structure and affects *Drosophila* reproduction. The results of this study showed female *Drosophila* that received HSD treatment produced few mature eggs resulting in decreased eggs hatching. Consumption of HSD in female *Drosophila* will cause decreased viability of eggs to hatch. HSD treatment also decreased hatching of *Drosophila* eggs. Excess glucose which is not needed by the tissues will lead to increased cellular degeneration, decreased fertility associated with low hatchability of *Drosophila* eggs.

Based on the results of DMRT calculations for hemolymph glucose and triglyceride levels, the female and male *Drosophila* groups in the *C vulgaris* extract treatment were not significantly different from the *Drosophila* control group. However, the female Drosophila group generally showed higher hemolymph glucose and triglyceride levels than the male *Drosophila* group (Table 1.). The intolerance mechanism of glucose and T2DM in mammals is caused by metabolic changes such as enzymatic dysregulation and increased glucose and triglycerides (Ecker *et al*., 2017). *Drosophila* that was given a double treatment of *C*. *vulgaris* extract and HSD showed improvements in glucose and triglyceride levels as a result of its work in regulating appetite and reducing HSD intake. Furthermore, the results of this study indicate a close relationship between increased glucose and triglycerides and increased oxidative stress in *Drosophila*. In a condition that excessive consumption of sucrose inhibits the formation of satiety signals in the brain, resulting in the release of more glucose into the body (Rovenko *et al*., 2015). The researchers observed that the effect of dietary manipulation such as HSD in *Drosophila* will have different responses according to gender (Castellanos *et al*., 2013). HSD treatment of female *Drosophila* clearly shows an increase in hemolymph glucose and triglyceride levels (Buescher *et al*., 2013).

CONCLUSION

The conclusion of the study show that *C*. *vulgaris* extract has various action in *Drosophila* metabolism. It acts mainly by its increasing in satiety, responding in reduce of

glucose and triglyceride levels in HSD-induced hyperglycemic *Drosophila*. Moreover, the results show the pharmacological potential of *C. vulgaris* extract against metabolic disorders such as T2DM. We suggest that further studies are needed to analyze the cellular and physiological mechanism of *C. vulgaris* extract against HSD causing T2DM disease.

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