Effects of *Ulva lactuca* mixed with *Spirulina platensis* on Creatinine and Ureum Levels in Central Obesity Patients

Putri Juanti[1], Jumasni Adnan[1], Hardiyanti Syarif[1], Maulita Indrisari[2], Marianti A.Manggau[1], Veni Hadju[3]*

[1] Departement Pharmacy, Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
[2] Faculty of Medicine, Palangka Raya University, Palangka Raya, Indonesia
[3] Departement of Nutrition, Faculty of Public health, Hasanuddin University, Makassar, Indonesia

**Corresponding Author:* putrijuantiapt@unhas.ac.id

ABSTRACT

Background: Obesity is rising rapidly and is expected to reach 40% by 2030, meaning nearly one in two adults will be obese. Nationally, the prevalence of central obesity has increased significantly, from 18.8% in 2007 to 26.6% in recent years. This study aims to determine the effect *Ulva lactuca* mixed with *Spirulina platensis* on creatinine and ureum levels in central obesity patients. Materials and Methods: Its study was a quasi-experimental design with a pretest-posttest control group. This research was carried out in two locations, Soppeng and Makassar, respectively, for intervention and control groups. Subjects were central obese with BMI over 25. One group received simple education and nori 3 g three times a day for 12 days (IG, n=20), while another only received simple education (CG, n=20). To evaluate the variance between groups, a paired t-test and an independent t-test have been used. Results: showed that most subjects were women (87.5 %) and home wives (67.5%). After the intervention, creatinine serum decreased in IG groups (0.889 mg/dL to 0.783 mg/dL, $p<0.05$ for IG and 0.807 mg/dL to 0.836 mg/dL, $p=0.083$ for CG). In addition, changes between groups were significant (0.106 mg/dL vs. 0.030 mg/dL, $p<0.05$). Similarly, ureum serum decreased in IG groups after interventions (50.770 mg/dL to 42.485 mg/dL, $p<0.05$ for IG and 48.600 mg/dL to 50.200 mg/dL, $p=0.247$ for CG). Changes between groups were also significant (8.285 mg/dL vs. 1.600 mg/dL, $p<0.05$). Conclusion: *Ulva lactuca* mixed with *Spirulina platensis* are 3 g three times a day for 12 days could decrease creatinine and ureum levels in central obesity patients.

Keywords: *Ulva lactuca, Spirulina platensis,* Central obesity, creatinine, Ureum.

INTRODUCTION

A study states that obesity in Indonesia is increasing every year and it is estimated that by 2030 it will increase to 40 percent, which means that almost 1 out of every 2 adults in Indonesia will be obese. Based on Riskesdas in 2013, the prevalence of central obesity nationally was 26.6%, an increase from 2007 which was 18.8% (JR and Syahrizal, 2021). Obesity is an excessive accumulation of fat due to an imbalance of energy intake with energy used (energy expenditure) for a long time which results in an increase in energy storage (Dipiro *et al.*, 2015).

Obesity is more at risk of worsening health conditions such as diabetes and decreased kidney function. Central obesity is a condition in which abnormal fat accumulation occurs (JR and Syahrizal, 2021). Central obesity, also known as visceral type, is a condition in which the accumulation of fat is excessive and far exceeds normal in the abdominal area. In Indonesia,

the highest prevalence of central obesity is in North Sulawesi, Gorontalo, and DKI Jakarta, respectively 31.5%, 27%, and 27.9% (Agustina, 2019).

This study began with research related to the development of obesity conditions, especially central obesity which increases with age, where this condition can trigger the development of serious degenerative diseases, especially those related to decreased kidney function, namely diabetic nephropathy. The mechanism of kidney damage that often occurs is due to the production of reactive oxygen species (ROS), so antioxidant therapy is one of the most promising as nephroprotective (Rodriguez S, *et al* 2017). This is the basis for the discovery of new drugs which are expected to be a solution for researchers. Aging or oxidative stress makes the human body gradually lose this dynamic balance and accumulate free radicals and reactive oxygen species (ROS) in the body. Free radicals and excessive ROS are the cause of various diseases such as tumors, neurodegenerative diseases, cardiovascular disease (CVD), diabetes, and organ damage (Han *et al.*, 2021).

The development of the pharmaceutical world related to new compounds found in marine waters has increased along with the number of discoveries made. Seaweed has recently received a lot of attention due to its potency and chemical composition. One of them is macroalgae, namely green algae (Chlorophyta) *Ulva lactuca* which has potential activity as an antioxidant, antimicrobial, antitumor, anticoagulant, anti-inflammatory, antihyperlipidemic, hypocholesterolemic, hepatoprotective, nephroprotective and as a prebiotic in the food industry. *Spirulina platensis* has therapeutic potential as a nephroprotective due to its antioxidant properties (Hernández-Lepe *et al.*, 2019).

Based on the chemical compounds contained in *Ulva lactuca* mixed with *Spirulina platensis* which is believed to improve the decrease in kidney function, it is necessary to conduct research on the benefits and efficacy of *Ulva lactuca* mixed with *Spirulina platensis* against decreased kidney function in terms of blood ureum and creatinine levels. If it is proven that *Ulva lactuca* mixed with *Spirulina platensis* can improve the decrease in kidney function, it is hoped that *Ulva lactuca* mixed with *Spirulina platensis* can be used as an alternative medicine in improving kidney function decrease.

METHODOLOGY

Sample and Research Location

This study is an experimental clinical trial that aims to determine the effectiveness of *Ulva lactuca* mixed with *Spirulina platensis* on the improvement of kidney function based on serum creatinine and serum ureum values of centrally obese patients. This test involves a population of centrally obese patients marked by a value of to be categorized as overweight or obese (25 kg/m2 BMI), aged between 35 and 65 as many as 20 participants as a treatment group (intervention) in the working area of Batu-batu Public health center, Batu-batu, Manorang salo, Marioriawa District, Soppeng Regency, South Sulawesi Province and 20 participants as a control group in the working area of Paccerakang Daya Public Public health center Makassar City, South Sulawesi Province.

Inclusion criteria consisted of the participant's habit of not taking any dietary supplements or drugs for 1 month during the study, no known medical problems or illnesses, and no smoking or alcohol consumption. Inclusion criteria included centrally obese patients with a BMI value above 25 which is indicated by an increase in serum ureum and serum creatinine values from normal values, and the patient's age is between 35-65 years.

Participants gave consent before the study was conducted by signing the informed consent and were willing to follow the test follow-up schedule.

Exclusion criteria included patients with type 1 and type 2 diabetes and/or taking insulin, CKD, typhoid fever, patients who were hypersensitive to any of the components of the test material, patients who were not taking degenerative drugs, and patients with severe disease complications. This research was conducted in September 2022.

Material Research

Ulva lactuca mixed with *Spirulina platensis* preparations came from the laboratory of the Faculty of Pharmacy, Hasanuddin University. *Ulva lactuca* samples were obtained from the Takalar Brackish Water Culture Hall and *Spirulina platensis* (*Arthrospira platensis)* was purchased in powder form. The powder form is packaged in one-time doses of 3 grams of *Ulva lactuca* mixed with *Spirulina platensis* (dose according to pre-clinical tests). The comparison of *Ulva lactuca* and *Spirulina platensis* is 10:1, that is, for every 6 grams of *Ulva lactuca* is added 0.6 grams of *Spirulina platensis*.

Preparation

The researcher collected participants in 2 research locations (Soppeng and Makassar) based on the inclusion criteria. Participants have also explained the course of the research and the rules of the research. Information was provided to participants during the treatment group in Soppeng, while the control group was conducted face-to-face in Makassar. Health workers in all locations participated in helping the research to run conducive. All participants in each group were willing to follow the researcher's directions, namely being willing to follow the direction of the ongoing research and giving consent by signing the informed consent.

Researchers also provide education related to balanced nutrition "Isi Piringku" through social media WhatsApp or SMS every 3 days during the research. Participants' food menu is expected to be in the form of foods rich in protein and carbohydrates. Participants were asked to record food every day during the study. In addition, participants in both groups submitted a 10-day food log on D-11 at baseline blood sampling and a 12-day supplementary food record to record macronutrient consumption throughout the study protocol. All research protocols have been approved by the local government of both Soppeng and Makassar.

Study Design

The test design method used is a quasi-experimental design with a pretest-posttest control group design. This research group was divided into 2 groups, namely control (CG) and treatment/intervention (IG). The number of subjects in each group was 20 patients. All study groups consumed the food menu 3 times a day. At the initial stage for 10 days, all patients in each group consumed food according to the education given once every 3 days. In the second stage for 12 days, only the treatment group (intervention) was given 3 grams of *Ulva lactuca* mixed with *Spirulina platensis* to be consumed together with food each patient eats in a day.

Before the basic measurements, the subjects were fully acquainted with all the tests and experimental procedures. As an initial control, after the diet was carried out according to the research rules, all study groups fasted for 8 hours without doing physical activity and initial measurements of blood samples were taken as D-11. Furthermore, all groups continued their diet for 12 days, namely from D-11 to D-22. For the treatment group, each meal was added

Ulva lactuca mixed with *Spirulina platensis* (Bagheri *et al.*, 2022). On D-23 all study groups fasted again for 8 hours without doing physical activity and the last blood sample was measured. The duration of the intervention was 23 days.

Outcomes Parameters and Data Analysis

Laboratory parameters used to assess nephroprotective activity on kidney function are serum creatinine and serum ureum values. Laboratory examinations were carried out at the Regional Health Laboratory (Labkesda) in Soppeng for the intervention group and the Health Laboratory Center (BBLK) of the Ministry of Health in Makassar for the control group. Clinical symptoms and possible side effects were also observed.

We recruited an additional 20% of participants (twenty subjects per group) so that a total of forty-eight participants were pooled to ensure that we reached our target sample size in the event of a potential failure during the study. The normality of the data was confirmed using the Shapiro-Wilk test. Independent T-Test analysis test and Mann-Whitney test were used for group comparison at baseline. Paired T-Test analysis test was used to compare the pretest-posttest of each group. Then to find out the difference between the intervention group and the control group, the Independent T-Test sample analysis test from Microsoft Excel 2019. Statistical significance was set at $p<0.05$. All analyzes were performed using Microsoft Excel 2019, SPSS (version 27.0), and Graphpad Prism (version 9.4.1).

RESULTS AND DISCUSSION

Result

Sample description

Table 1 – characteristics of the study subjects, 35-year-old to 65 years old, men and women (total n = 40).

	IG		CG	
	n	**%**	**n**	**%**
Sample size	20	50	20	50
Sex				
Male	4	20	1	5
Female	16	80	19	95
Age (Years)				
35 – 44	11	55	2	10
45 – 54	7	35	11	55
55 – 65	2	10	7	35
Education				
Junior High School	5	25	2	10
Senior High School	10	50	7	35
Bachelor	4	20	11	55
Master	1	5	0	0

The characteristics of the research sample can be seen in table 1. The number of participants was 20 for IG and also 20 for CG from the total sample were women (80% = IG,

95% = CG) and men (20% = GI, 5% = CG). Age group 35-44 years 11 participants (IG) and 2 participants (CG), 45-54 years 7 participants (IG) and 11 participants (CG), and 55-65 years 2 participants (IG) and 7 participants (CG). About 50% of the intervention group were high school graduates and 55% of the control group were undergraduates. Results showed that most of the subjects were women (87.5%) and home wives (67.5%).

No side effects were reported from the supplementation of *Ulva Lactuca* mixed with *Spirulina platensis*. All participants in both groups consumed food according to the education given by "fill my plate", namely 1/3 of half plate of fruits, 1/3 of half plate of side dishes, 2/3 of half plate of staple foods (carbohydrates) and 2 /3 of a half plate of vegetables on days 1-10 of the start of the study. Control group participants consumed more fat, protein, and carbohydrates on days 11-22 compared to days 1-10. Participants in both groups did not have strenuous activities, on average the participants were housewives and civil servants.

Table 2 – Baseline of the study subjects

BASELINE	IG	CG	p-value
	Mean ± SD	Mean ± SD	
Weight (kg)	70.058 ± 6.507	65.355 ± 8.510	p = 0.057
Height (cm)	151.99±7.311	150055±6.658	p = 0.387
Waist circumference (cm)	90.735±4.416	95.870 ± 6.538	P<0.05
Creatinine (mg/dL)	0.889 ± 0.128	0.807 ± 0.100	p = 0.030
Ureum (mg/dL)	50.770 ± 5.668	48.600±4.160	p = 0.176

Table 2 is the initial data from the study which is data taken on D-11. The data included body weight, height, abdominal circumference, serum creatinine, and serum ureum values from each study group. The table above shows that participants in all groups have almost the same average value or there were not many differences. The results of all data in table 2 have been tested for normality using the test Shapiro-Wilk where spss (ver.27.0) is normally distributed except for the waist circumference of the IG. The average body weight in the intervention group was 70,058 kg (SD ±6.507) was greater than the control group was 65.355 kg (SD ±8.510) with p-value = 0.057, which means that there was no significant difference, so it can be said that the basic data values in the two groups had no difference. The average height in both groups when viewed from the data in table 2, the intervention group was 151.99 cm (SD ± 7.311) and the control group was 150.055 cm (SD ± 6.658), p=0.387, meaning there was no significant difference between the two groups.

While the different results in the mean waist circumference of the treatment group 90.735 cm (SD ± 4.416) and the control group 95.870 cm (SD ± 6.538), there was a difference between the intervention group and the control group as initial data with p<0.05. In addition, the above values are also used as the basis for selecting participants who are included in the inclusion criteria in the study by looking at BMI values above 25.

On the other hand, the mean serum creatinine value in the two groups was not significantly different as the initial data for participants on day 11 for the intervention group was 0.889 mg/dL (SD ±0.128) and the control group was 0.807 mg/dL (SD ±0.100) with p=0.030. Similarly, the mean serum ureum value at the beginning of the measurement there was no significant difference between the two groups, the serum ureum value was 50.770 mg/dL (SD

± 5.668) for the intervention group and the serum ureum value was 48.600 mg/dL (SD ± 4.160) for the control group with p=0.176.

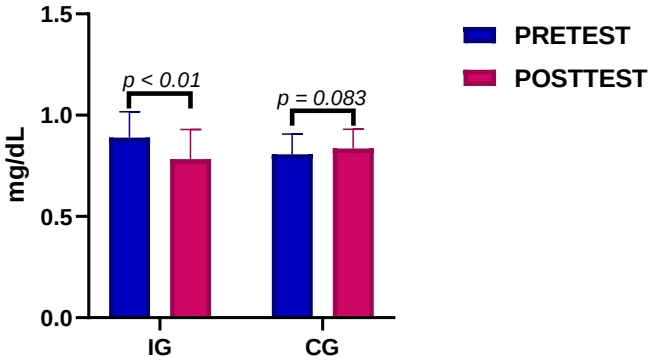

Figure 1. Serum creatinine values before and after intervention on IG and CG.

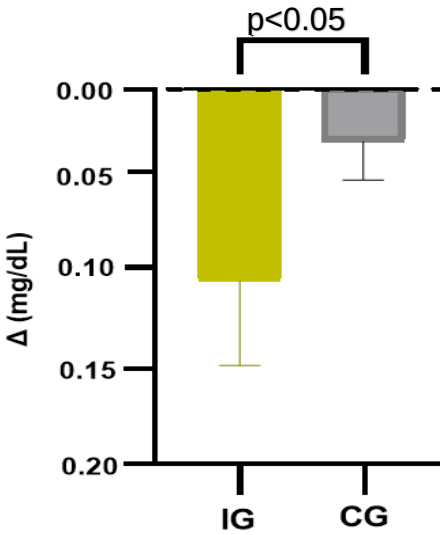

Figure 2. Difference in serum creatinine values

The result of data taken from the initial examination of blood samples of D-11 participants as pretest data and the final examination of blood samples of D-23 participants as posttest data. As seen in figure 1, the serum creatinine values in the two groups were different. In the intervention group, the mean value before intervention (pretest) was 0.889 mg/dL (SD ±0.128) while the mean value after intervention (posttest) was 0.106 mg/dL (SD ±0.146) with p<0.05. in the control group, the mean value before intervention (pretest) was 0.807 mg/dL (SD ±0.100) while the mean value after intervention (posttest) was 0.836 mg/dL (SD ±0.095) with p=0.083. Testing in one group (pretest and posttest) was carried out with paired t-test analysis to compare before and after the intervention. The difference between before and after the intervention was 0.106 mg/dL (SD ±0.046) for the treatment group and 0.030 mg/dL (SD ±0.021) for the control group. The results of the difference in serum creatinine intervention were then analyzed using independent t-test with p<0.05.

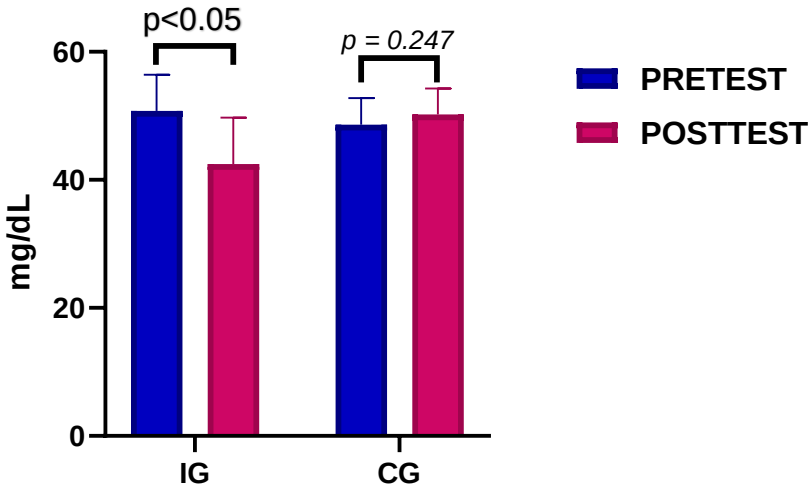

Figure 3. Serum ureum values before and after intervention on GI and CG.

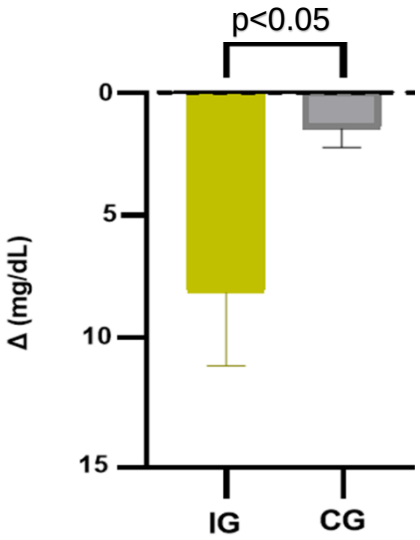

Figure 4. Difference in serum ureum values

Similarly, the serum ureum values in the two groups were different. In the intervention group, the mean value before intervention (pretest) was 50.770 mg/dL (SD ± 5.668) while the mean value after intervention (posttest) was 42.485 mg/dL (SD ± 7.263) with p<0.05. in the control group the mean value before intervention (pretest) was 48.600 mg/dL (SD ±4.160) while the mean value after intervention (posttest) was 50.200 mg/dL (SD ±4.072) with p-value = 0.247. Testing in one group (pretest and posttest) was carried out with paired t-test analysis to compare before and after intervention. The difference between before and after intervention was 8.285 mg/dL (SD ±2.988) for the treatment group and 1.600 mg/dL (SD ±0.754) for the control group.

DISCUSSION

This study evaluated changes in serum creatinine and serum ureum levels as markers of renal function in centrally obese patients with or without intervention of *Ulva lactuca* mixed with *Spirulina platensis*. Based on the results of the study, the most visible observation in the comparison of the intervention group (IG) data was that it could significantly reduce serum creatinine levels by 0.106 mg/dL (SD ±0.046) and serum ureum by 8.285 mg/dL (SD ±2.988)

centrally obese participants. In addition, the results of GI observations with the intervention were more significantly different than without the intervention, with the value before the intervention of serum creatinine levels from 0.889 mg/dL (SD ±0.128) to 0.783 mg/dL (SD ±0.146) with $p<0.05$ indicating that there is a significant difference between before and after intervention. Similarly, regarding changes in serum ureum levels, the results of the GI study after intervention showed a significant difference compared to no intervention ($p<0.05$) from 50.770 mg/dL (SD ± 5.668) to 42.485 mg/dL (SD ± 7.263). Even though in reality the control group was also able to reduce the serum creatinine value, there was no significant difference ($p = 0.083$) and the serum ureum value was also ($p = 0.247$). Therefore, the results of this study are important because we demonstrated that *Spirulina platensis* mixed with *Ulva lactuca* has the potential to significantly lower serum creatinine and serum ureum levels in centrally obese patients.

Central obesity reflects high levels of intra-abdominal or visceral fat associated with the development of degenerative diseases and comorbidities (Dipiro *et al.*, 2015). The etiology of obesity may be multifactorial and related to various contributions from genetic factors that are one of the main determinants of obesity, in addition to environmental factors, namely reduced physical activity and work, consuming excessive and high-fat foods, and lifestyle. Obesity can also be caused by the use of drugs such as corticosteroids and insulin as well as the number of neurotransmitters and neuropeptides that stimulate appetite in brain tissue which affects total calorie intake (Dipiro *et al.*, 2015). Body mass index (BMI) and waist circumference (WC) can be used as markers of excess body fat that independently predict disease risk (Yousefi, Mottaghi and Saidpour, 2018). Abdominal circumference is a simple measurement and is an approximate index of intra-abdominal fat mass and total body fat (JR and Syahrizal, 2021). AC size Central obesity in men > 90 cm and women > 80 cm (Moradi *et al.*, 2019). Adrenergic stimulation activates lipolysis in fat cells and increases energy expenditure in adipose tissue and skeletal muscle. Plasma creatinine kinase is an independent marker of BMI as well as a measure of abdominal obesity (Dipiro *et al.*, 2015).

Skeletal muscle tissue and creatinine kinase have been associated with obesity, insulin resistance, and decreased capacity to increase resting metabolic rate after overeating (Han *et al.*, 2021). Plasma creatinine kinase and obesity are biologically interrelated because the enzyme creatinine kinase functions to regulate key metabolic processes leading to the entry and oxidative catabolism of glucose and lipids in skeletal muscle fibers (Haan *et al.*, 2017). Increased levels of creatinine and ureum show adverse effects on several kidney functions resulting in the inability of the kidneys to clear the waste products of muscle metabolism from the blood as well as a decrease in glomerular filtration activity so that proteins and cells are retained and not excreted in the urine (Khalil *et al.*, 2020). The creatinine test is a reliable test for estimating the glomerular filtration rate (Abdel-Daim *et al.*, 2019). While the determination of ureum levels aims to measure the amount of ureum, which is a waste product of protein metabolism in the blood where ureum is removed from the bloodstream through the kidneys. Blood Ureum Nitrogen (BUN) test is a test that determines the amount of ureum in the blood and can be used to test kidney function (Wicaksono, 2019).

Gamma irradiation markedly decreases serum protein and albumin levels while increased serum creatinine and ureum levels are a response to whole-body gamma irradiation indicating kidney damage or impairment (Aziz *et al.*, 2018). Elevated creatinine levels may be due to back leakage of filtered creatinine through the injured tubular epithelium. increased oxidative deamination of amino acids in the liver resulting in excessive ureum production or due to radiation damage to the detoxification function of the liver. In addition, the increase in serum ureum level which is the main end product of protein catabolism may also be caused by

excessive protein degradation after irradiation (Aziz *et al.*, 2018). High glucose levels will result in high oxidative stress (Wu *et al.*, 2020). Oxidative stress is a condition that occurs when the production of reactive oxygen species (ROS) exceeds the resulting antioxidant defenses against them (Ghareeb *et al.*, 2021). Reactive oxygen species (ROS) are key factors causing many diseases in the human body because reactive species/free radicals can induce damage to cellular proteins, DNA, and lipid membranes (Yang *et al.*, 2021). ROS can cause an increase in ureum and creatinine levels. Increased plasma creatinine and ureum levels indicate a decrease in the glomerular filtration rate and consequently decreased kidney function (Kammoun *et al.*, 2018). Reactive oxygen species (ROS) are key factors causing many diseases in the human body because reactive species/free radicals can induce damage to cellular proteins, DNA, and lipid membranes (Abdel-Daim *et al.*, 2019).

Polysaccharides from seaweed have been shown to have significant antioxidant activity both in vivo and in vitro (Uribe *et al.*, 2019). Some of the activities of these polysaccharides include protective action against oxidative stress that triggers kidney damage (Reis *et al.*, 2020). *Ulva lactuca* belongs to the Chlorophyta group, namely green algae where *Ulva lactuca* is a species of green seaweed commonly known as sea lettuce which is well consumed throughout the world because of its special nutritional value with a long history (Meinita, Harwanto and Choi, 2022). *Ulva lactuca* is a heterogeneous sulfate compound known as residual polysaccharide rhamnose, uronic acid galactose, mannose, galactose, arabinose, and glucose (Kammoun *et al.*, 2018).

Ulvan is a sulfated polysaccharide located in the cell walls of green algae that has been increasingly studied over the years for pharmaceutical applications (Tziveleka, Ioannou and Roussis, 2019). Ulvan exhibits physicochemical and biological activities and has the potential for pharmaceutical, food, chemical, and agricultural applications. Ulvan has finally received special attention in biomedical applications due to its high biocompatibility and no side effects (Don *et al.*, 2021). Both in vivo and in vitro experiments show that ulvan has antioxidants (Liu *et al.*, 2019). Polysaccharides from *Ulva lactuca* significantly improve glucose and lipid homeostasis in diabetes by delaying the digestion and absorption of carbohydrates and lipids by inhibiting enzymes in both the blood and small intestine. Therefore, polysaccharides from *Ulva lactuca* present a potentially useful dietary adjunct for the treatment of diabetes and obesity. In addition, polysaccharides from *Ulva lactuca* (ULPS) significantly protect renal function by lowering plasma creatinine, ureum, and albumin levels (Tair, Bensalah and Boukortt, 2018).

The repair effect of *Ulva lactuca* (UPE) polysaccharide extract on oxidative stress-induced kidney injury was analyzed. The results showed that *Ulva lactuca* polysaccharide extract could reduce serum creatinine (Scr), blood ureum nitrogen (BUN), serum cystatin C (Cys-C), lipid peroxidation, protein carbonylation, and DNA oxidative damage (8-OHdG) as well as repair kidney damage (Yang *et al.*, 2021). Co-administration of polysaccharides extracted from *Ulva lactuca* also led to significant renal recovery. This indicates that the nephroprotective activity of marine algae extract is possible due to its antioxidant activity and rich polysaccharides in protecting kidney tissue (Kammoun *et al.*, 2018). *Spirulina platensis* is a blue-green spiral microalga with a rich content of antioxidant active constituents, such as C-phycocyanin, Phycobiliproteins, and carotenoids also found in sulfated polysaccharide that act as free radical scavengers, and have strong antioxidant activity (Martins *et al.*, 2022). *Spirulina platensis* significantly lowers enzymes as markers of serum kidney function (creatinine and ureum) so the protective role of *Spirulina platensis* related to its hypoglycemic and nephroprotective effects can be proven (Ragheb and Aljehany, 2020). *Spirulina platensis* exhibits nephroprotective potential by modulating biomarkers of renal function and improving

renal histology (Khalil *et al.*, 2020). Reversible kidney damage, such as kidney infection, blockage of kidney stones, and decreased kidney function can be corrected by using *Spirulina platensis* (Aziz *et al.*, 2018). The protein contained in *Spirulina platensis* is mainly phycobiliprotein, which mainly consists of phycocyanin, allophycocyanin, and phycoerythrin. Phycocyanin is the most active bioactive substance in *Spirulina platensis* which contains 10% -20% of dry biomass (Han *et al.*, 2021). Phycocyanin is an active protein sulfated polysaccharide that has antioxidant properties (Islam and Sarkar, 2020)

Spirulina platensis and C-phycocyanin have shown therapeutic potential in kidney damage where oxidative stress is an important factor that triggers many diseases. These effects of *Spirulina platensis* and C-phycocyanin on the kidney are attributed to their antioxidant properties (DiNicolantonio, Bhat and OKeefe, 2020). Antioxidant activity of *Spirulina platensis* namely phycocyanin and phycocyanobilin which protect against diabetic nephropathy (Khalil *et al.*, 2020). *Spirulina platensis* minimizes nephrotoxic effects through its anti-inflammatory and antioxidant activities and the combination of both agents exhibits stronger antioxidant and nephroprotective effects than *Spirulina platensis* alone (Abdel-Daim *et al.*, 2019). *Spirulina platensis* exerts a glucose-lowering effect by combating gluconeogenesis and *Spirulina platensis* exhibits its antidiabetic effect by reducing oxidative stress, enhancing activity regulating transcription of antioxidant enzymes and normalizing pro-apoptotic and pro-inflammatory cytokine gene expression, possibly through higher content of natural antioxidant compounds (Han *et al.*, 2021). Chronic hyperglycemia in diabetes leads to an overproduction of free radicals, which contributes to the development of diabetic nephropathy. The antioxidant activity of phycocyanin is related to its specific structure, and the dark blue color is due to the open-structured chromophore of tetrapyrrole and phycocyanobilin covalently bound to the apoprotein (Ragheb and Aljehany, 2020). The chemical structure of phycocyanobilin is similar to that of bilirubin, a very specific inhibitor of triphosphopyridine nucleotide (NADPH) oxidase. This may be why phycocyanobilin inhibits NADPH oxidase (Han *et al.*, 2021).

CONCLUSION

This study showed that *Ulva lactuca* mixed with *Spirulina platensis* are 3 g three times a day for 12 days may decrease creatinine serum and ureum serum in central obesity patients that were able to improve kidney function as determined by observations of laboratory results. Further studies are needed to ensure a decrease in serum creatinine and serum ureum values with a larger number of participants and the duration of the intervention is up to 1-3 months. Therefore, this study is expected to provide new information for the public about the benefits of *Ulva lactuca* mixed with *Spirulina platensis* can be used as a health food supplement product in public health implications in improving kidney function decrease.

REFERENCES

Abdel-Daim, M.M. *et al.* (2019) 'Influence of Spirulina platensis and ascorbic acid on amikacin-induced nephrotoxicity in rabbits', *Environmental Science and Pollution Research*, 26(8), pp. 8080–8086. Available at: https://doi.org/10.1007/s11356-019-04249-4.

Agustina, W. (2019) 'PENGARUH OBESITAS SENTRAL TERHADAP STATUS KESEHATAN KARYAWAN STIKES MAHARANI DI KOTA MALANG', *Jurnal Ilmiah Kesehatan Media Husada*, 8(1), pp. 01–11. Available at: https://doi.org/10.33475/jikmh.v8i1.184.

Aziz, M.M. *et al.* (2018) 'Possible protective effect of the algae spirulina against nephrotoxicity induced by cyclosporine A and/or gamma radiation in rats', *Environmental Science and Pollution Research*, 25(9), pp. 9060–9070. Available at:

https://doi.org/10.1007/s11356-017-1146-0.

Bagheri, R. *et al.* (2022) 'Spirulina supplementation during gradual weight loss in competitive wrestlers', *British Journal of Nutrition*, 127(2), pp. 248–256. Available at: https://doi.org/10.1017/S000711452100091X.

DiNicolantonio, J.J., Bhat, A.G. and OKeefe, J. (2020) 'Effects of spirulina on weight loss and blood lipids: a review', *Open Heart*, 7(1), p. e001003. Available at: https://doi.org/10.1136/openhrt-2018-001003.

Dipiro, J. *et al.* (2015) *Pharmacotherapy Handbook: Nutrition Support Obesity*. Ninth Edition. Edited by Dipiro CV. McGraw-Hill Education.

Don, T.-M. *et al.* (2021) 'Crosslinked complex films based on chitosan and ulvan with antioxidant and whitening activities', *Algal Research*, 58, p. 102423. Available at: https://doi.org/10.1016/j.algal.2021.102423.

Ghareeb, D.A. *et al.* (2021) '*Ulva lactuca* methanolic extract improves oxidative stress-related male infertility induced in experimental animals', *Archives of Physiology and Biochemistry*, 127(5), pp. 397–405. Available at: https://doi.org/10.1080/13813455.2019.1645698.

Haan, Y.C. *et al.* (2017) 'Creatine kinase as a marker of obesity in a multi-ethnic population', *Molecular and Cellular Endocrinology*, 442, pp. 24–31. Available at: https://doi.org/10.1016/j.mce.2016.11.022.

Han, P. *et al.* (2021) 'Anti-oxidation properties and therapeutic potentials of spirulina', *Algal Research*, 55, p. 102240. Available at: https://doi.org/10.1016/j.algal.2021.102240.

Hernández-Lepe, M.A. *et al.* (2019) 'Hypolipidemic Effect of Arthrospira (Spirulina) maxima Supplementation and a Systematic Physical Exercise Program in Overweight and Obese Men: A Double-Blind, Randomized, and Crossover Controlled Trial', *Marine Drugs*, 17(5), p. 270. Available at: https://doi.org/10.3390/md17050270.

Islam, M. and Sarkar, S. (2020) 'Hypoglycemic Effects of Spirulina platensis (Spirulina platensis) Leaves in Normal and Aloxan Diabetic Rat', *', Agriculture, Livestock And Fisheries*, 7(3), pp. 475-479.

JR, T. and Syahrizal (2021) 'Central Obesity with Hyperglycemia Incidence in Regional Work Unit Employees', *Higeia Journal Of Public Health Research And Development*, 5(3), pp. 354–364.

Kammoun, I. *et al.* (2018) 'Hypolipidemic and cardioprotective effects of *Ulva lactuca* ethanolic extract in hypercholesterolemic mice', *Archives of Physiology and Biochemistry*, 124(4), pp. 313–325. Available at: https://doi.org/10.1080/13813455.2017.1401641.

Khalil, S.R. *et al.* (2020) 'Protective effect of Spirulina platensis against physiological, ultrastructural and cell proliferation damage induced by furan in kidney and liver of rat', *Ecotoxicology and Environmental Safety*, 192, p. 110256. Available at: https://doi.org/10.1016/j.ecoenv.2020.110256.

Liu, X. *et al.* (2019) 'Anti-ageing and antioxidant effects of sulfate oligosaccharides from green algae Ulva lactuca and Enteromorpha prolifera in SAMP8 mice', *International Journal of Biological Macromolecules*, 139, pp. 342–351. Available at: https://doi.org/10.1016/j.ijbiomac.2019.07.195.

Martins, B. *et al.* (2022) 'Biological Potential, Gastrointestinal Digestion, Absorption, and Bioavailability of Algae-Derived Compounds with Neuroprotective Activity: A Comprehensive Review', *Marine Drugs*, 20(6), p. 362. Available at: https://doi.org/10.3390/md20060362.

Meinita, M.D.N., Harwanto, D. and Choi, J.-S. (2022) 'Seaweed Exhibits Therapeutic Properties against Chronic Diseases: An Overview', *Applied Sciences*, 12(5), p. 2638. Available at: https://doi.org/10.3390/app12052638.

Moradi, S. *et al.* (2019) 'Effects of Spirulina supplementation on obesity: A systematic review and meta-analysis of randomized clinical trials', *Complementary Therapies in Medicine*, 47, p. 102211. Available at: https://doi.org/10.1016/j.ctim.2019.102211.

Ragheb, E.M. and Aljehany, B.M. (2020) 'Evaluation of the Ameliorative Effects of Spirulina in PropylthiouracilInduced Hyperlipidaemia, Liver and Kidney Toxicity in Rats', *Journal of Pharmaceutical Research International*, pp. 21–31. Available at: https://doi.org/10.9734/jpri/2020/v32i2630836.

Reis, S.E. *et al.* (2020) 'Influence of sulfated polysaccharides from Ulva lactuca L. upon Xa and IIa coagulation factors and on venous blood clot formation', *Algal Research*, 45, p. 101750. Available at: https://doi.org/10.1016/j.algal.2019.101750.

Rodriguez-Salgueiro, S., Ramirez-Carmenate, Z. and Gonzalez-Nunez, L. (2017) 'An Update on Potential Applications of Spirulina platensis and C-Phycocyanin to Treat Kidney Diseases ', *Annals of Research in Antioxidants*, 2(1).

Tair, Z.I., Bensalah, F. and Boukortt, F. (2018) 'Effet de la supplémentation des polysaccharides de l'algue verte Ulva lactuca sur la pression artérielle et sur les facteurs du risque athérogène, chez des rats consommant un régime riche en lipides', *Annales de Cardiologie et d'Angéiologie*, 67(3), pp. 133–140. Available at: https://doi.org/10.1016/j.ancard.2018.04.016.

Tziveleka, L.-A., Ioannou, E. and Roussis, V. (2019) 'Ulvan, a bioactive marine sulphated polysaccharide as a key constituent of hybrid biomaterials: A review', *Carbohydrate Polymers*, 218, pp. 355–370. Available at: https://doi.org/10.1016/j.carbpol.2019.04.074.

Uribe, E. *et al.* (2019) 'Effect of different drying methods on phytochemical content and amino acid and fatty acid profiles of the green seaweed, Ulva spp.', *Journal of Applied Phycology*, 31(3), pp. 1967–1979. Available at: https://doi.org/10.1007/s10811-018-1686-9.

Wicaksono, S. (2019) 'The Effect of Oral Administration of Spirulina platensis Given Ccl4 on Ureum and Creatinine Levels in White Rat Blood', *Journal of Health*, 12(2), pp. 86–91.

Wu, D. *et al.* (2020) 'Structural characterization and hypoglycemic effect of green alga Ulva lactuca oligosaccharide by regulating microRNAs in Caenorhabditis elegans', *Algal Research*, 51, p. 102083. Available at: https://doi.org/10.1016/j.algal.2020.102083.

Yang, Q. *et al.* (2021) 'Protective Effects of Ulva lactuca Polysaccharide Extract on Oxidative Stress and Kidney Injury Induced by D-Galactose in Mice', *Marine Drugs*, 19(10), p. 539. Available at: https://doi.org/10.3390/md19100539.

Yousefi, R., Mottaghi, A. and Saidpour, A. (2018) 'Spirulina platensis effectively ameliorates anthropometric measurements and obesity-related metabolic disorders in obese or overweight healthy individuals: A randomized controlled trial', *Complementary Therapies in Medicine*, 40, pp. 106–112. Available at: https://doi.org/10.1016/j.ctim.2018.08.003.