Pharmacogn J. 2021; 13(4): 958-964
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Repairing of Renal Tubules in Diabetic Rats (*Rattus norvegicus*) Diabetes After Administration of Golden Sea Cucumber (*Stichopus hermanii*)

Herin Setianingsih*, Satria Erda Wisnumarta, Sareh Arjono Tjandra

ABSTRACT

This study aims to analyze the improvement of the histopathological picture of renal tubules in diabetic rats after being given golden sea cucumber extract (*Stichopus hermanii*). This research uses experimental design laboratories with a post-test only control group design method. The sampling used simple random sampling with 25 white rats divided into five groups, namely groups that were given standard feed without STZ-induced, STZ-induced group, STZ-induced group and given golden sea cucumber extract at a dose of 4.25 mg/kg BW for 21 days, STZ-induced group and given golden sea cucumber extract at a dose of 8.5 mg/kg BW for 21 days, and STZ-induced group and given gold sea cucumber extract at a dose of 12.75 mg/kg BW for 21 days. The data on the observation of each group's kidney histopathology was carried out at the end of the session. The results of the analysis using the Kruskal-Wallis Test showed significant results, the Mann-Whitney Test showed significant differences between the STZ-induced group and the golden sea cucumber extract (*Stichopus hermanii*) dose of 12.75 mg/kg BW (x=7.4 mg/dl) decreased significantly (p=0.001) compared to the STZ-only-induced group (x=12.6 mg/dl). Administration of golden sea cucumber extract (*Stichopus hermanii*) at a dose of 12.75 mg/kg BW of rats for 21 days lowered the degree of tubular damage to the kidney rectus of white rats (*Rattus norvegicus*) male streptozotocin-induced strains.

Key words: Tubular injury, Diabetic rat, *Stichopus hermanii*.

Herin Setianingsih*, Satria Erda Wisnumarta, Sareh Arjono Tjandra

Faculty of Medicine, Universitas Hang Tuah, Surabaya, INDONESIA.

Correspondence

Herin Setianingsih

Faculty of Medicine, Universitas Hang Tuah, Surabaya, INDONESIA.

Phone no: +(62)31843875

Fax: +(62)318433626

E-mail: herin.setianingsih@hangtuah.ac.id

History

- Submission Date: 17-03-2021;
- Review completed: 11-04-2021;
- Accepted Date: 24-05-2021.

DOI : 10.5530/pj.2021.13.123

Article Available online

http://www.phcogj.com/v13/i4

INTRODUCTION

Diabetes is one of the largest diseases suffered by the world's population. Today, approximately 422 million people with Diabetes who are 18 years old worldwide or 8.5% of the entire world population[1,2,3]. In Indonesia, RISKESDAS data shows an increase in the prevalence of Diabetes Indonesia from 5.7% in 2007 to 6.9% or about 9.1 million in 2013. Sample Registration Survey data in 2014 showed that diabetes is the number 3 leading cause of death in Indonesia with a percentage of 6.7%, after Stroke (21.1%), and Coronary Heart disease (12.9%)[4]. One of the complications of Diabetes Mellitus will develop into diabetic nephropathy. Diabetic nephropathy occurs due to blood sugar levels resulting in abnormalities in the kidney blood vessels. If in the advanced stage, this diabetic nephropathy condition will result in patients experiencing chronic kidney injury (CKD) that requires replacement treatment with blood washing (haemodialysis). Nearly 20-30 percent of people with diabetes mellitus will experience diabetic nephropathy, which then becomes chronic renal failure[5].

Indonesia is a country with a larger water area than the land area; therefore, Indonesia was referred to as a Maritime State. Even the potential of seafood owned by Indonesia certainly has the best quality[6,7]. The widespread of coral reefs makes Indonesia the country with the largest sea cucumber potential and the world's largest sea cucumber exporter, which is mostly used as a food industry commodity and exported to other countries, especially in east Asia such as Hongkong[8].

This research makes use of this abundant biota. Until now, Indonesia has not been able to process sea cucumbers into products that provide more benefits. For example, in medicine, golden sea cucumbers also have high antioxidant activity to ward off free radicals[9]. Support for the trust of local people in the archipelago such as in Malaysia who believe that commercial dry sea cucumbers and smoked sea cucumbers have properties that can cure various diseases such as cancer, asthma, hypertension, rheumatism, skin damage, and degenerative diseases[10].

Damayanti research shows that golden sea cucumber water extract contains antioxidant content beneficial to the body, such as flavonoids, saponins, amino acids, zinc minerals, and others[11]. Ismantoro *et al.* showed the results of his study using male rats strain Wistar, which was given sea cucumber extract therapy then induced toxic material, namely paracetamol obtained the effect of sea cucumbers as nephroprotective. Histopathological images of vital organs in these animals prove that golden sea cucumbers can help repair body tissues[12]. Based on the study above, this study analyzed improvements in the histopathological picture of tubules renal kidneys in diabetic rats after being given golden sea cucumber extract (*Stichopus hermanii*).

Cite this article: Setianingsih H, Wisnumarta SE, Tjandra SA. Repairing of Renal Tubules in Diabetic Rats (*Rattus norvegicus*) Diabetes After Administration of Golden Sea Cucumber (*Stichopus hermanii*). Pharmacog J. 2021;13(4): 958-964.

MATERIALS AND METHODS

This research is an experimental research laboratory using a post-test only group design method. The research was conducted at the Embryology Laboratory of the Faculty of Veterinary Medicine, Universitas Airlangga. The sample size used was 25 animals tried using the Federer formula with the criteria of a try animal that is 2-3 months old with 150-200 grams. All animals try the male white rat Wistar strain (*Rattus norvegicus*) conducted a research adaptation for seven days.

Ethical approval

This study was approved by the Commission of Faculty of Dental Medicine Health Research, Universitas Airlangga, Surabaya, Indonesia (No. 591/HRECC.FODM/IX/2019).

Manufacture of golden sea cucumber extract

Fresh golden sea cucumber (*Stichopus hermanii*) weighing 9 kg was taken from Sumenep Regency, precisely on Sapeken Island (an eastern archipelago of Madura Island), then identified in the Laboratory of Biosciences and Plant Technology Department of the Faculty of Natural Sciences Institut Sepuluh Nopember (ITS) then taken to Widya Mandala University, Surabaya for extraction stage:

Extract preparation

Golden sea cucumbers are cleaned, removed inside, and cut into pieces 3-10cm in size. Then dried in the oven at 50 °C. Dried golden sea cucumbers are smoothed with a blender into powder and gained a weight of 1.3 kg. Then, the golden sea cucumber powder is macerated by repeatedly stirring for 8 hours and soaked in an 80% ethanol solution for 24 hours. After that, an 80% ethanol solution was collected and gold sea cucumber pulp in maceration with 80% ethanol in the same way (total ethanol solution used as much as 5.5 liters). The 80% ethanol solution obtained is evaporated with a water temperature of 50 °C until the ethanol solution evaporates and obtains a thick extract of 242.5 grams of golden sea cucumber. Golden sea cucumber extract is added CMC-Na (Sodium Carboxymethyl Cellulose) until liquid.[13]

Selection and manufacture of streptozotocin (STZ) solutions

Streptozotocin (STZ) is a diabetogenic agent with toxic abilities that damages β cells.[14] The study was intended to create experimental diabetic conditions in male white rat (*Rattus norvegicus*) animals using the diabetogenic agent streptozotocin. Induction of streptozotocin hyperglycemia will be carried out by intraperitoneal STZ solution injection at a dose of 40-50 mg/kg BW.[15] STZ calculation for rats with an average weight of 175 grams. The manufacture of STZ solution using citrate buffer was then induced in rats intraperitoneally.[13]

CMC-Na manufacturing 1%

Make CMC-Na solution 1% utilizing 1 gr CMC-Na mixed with 100 ml aquadest, sprinkled evenly over aquadest, waited for approximately 15 minutes, and then stirred until perfectly dissolved. Administration of sonde one mL/150 gr BW animals.[16]

Pre-treatment stage

Injection of STZ at a 40 mg/kg BW[15]. In sodium citric buffer pH 4.5 administered intraperitoneally as much as 0.5 ml on day 1. Then an injection of STZ dose 50 mg/kg BW on the 14th day to make white rats experience a condition of hyperglycemia. An injection was performed by inserting a needle parallel to the rat's leg then pushed through the abdominal wall into the peritoneal cavity[17].

Treatment stage

Animals try to be divided into five groups, namely:

• Negative control (-): Group of white rats (*Rattus norvegicus*) who were given standard feed for 39 days.

• Positive control (+): Group of white rats (*Rattus norvegicus*) who were given standard feed, then on the 1st day, animals tried to inject STZ 40 mg/kg BW, then on the 14th day injected STZ dose 50 mg /kg BW. STZ is administered intraperitoneally in the morning to get the condition hyperglycemia on the 17th day.

• Treatment 1: White rat group (*Rattus norvegicus*) given standard feed, then on the 1st day, animals try to inject STZ 40 mg/kg BW, then on the 14th day injected STZ dose 50 mg/kg BW. STZ is administered intraperitoneally in the morning to get the condition hyperglycemia on the 17th day. On the 18th day, animals try to be given a gold sea cucumber extract dose of 4.25 mg/kg BW daily for 21 days.

• Treatment 2: White rat group (*Rattus norvegicus*) given standard feed, then on the 1st day, animals try to inject STZ 40 mg/kg BW, then on the 14th day injected STZ dose 50 mg/kg BW. STZ is administered intraperitoneally in the morning to get the condition hyperglycemia on the 17th day. On the 18th day, animals try to be given a gold sea cucumber extract dose of 8.5 mg/kg BW daily for 21 days.

• Treatment 3: Group of white rats (*Rattus norvegicus*) given standard feed, then on the 1st day, animals try to be injected STZ 40 mg/kg BW, then on the 14th day injected STZ dose 50 mg/kg BW. STZ is administered intraperitoneally in the morning to get the condition hyperglycemia on the 17th day.

• On the 18th day, the animal tried to be given a gold sea cucumber extract dose of 12.75 mg/kg BW daily for 21 days.

Preparation of histopathology

Kidney samples were sent and processed to the Department of Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Airlangga, to block paraffin and hematoxylin-eosin (HE) staining.

Histopathological observations

Histopathological preparation observations of the samples were conducted using a light microscope at a magnification of 400 times to see the entire view field. Then determine the area to be observed, i.e., in the kidneys part of the proximal tubular epithelial cell cortex. In the study of grading methods by Avdagic, there was discontinuation (damage) of epithelial cells and tubule necrosis. Necrosis is the death or swelling of endoplasmic and mitochondrial reticulum cells and the blistering of membranes. Necrosis is also characterized by loss of nucleus, increased eosinophils so that cells appear more glossy than normal cells triggered by external stimuli.[18,19]

Statistics analysis

Statistical analysis of this study was used to compare the histopathological picture of renal tubular epithelial cells that necrosis in each group of rats. The data collected was then statistically analyzed using the IBM SPSS (Statistical Product and Service Solution) through the Kruskall-Wallis test to determine whether there was proximal tubular cell damage among the research group. The degree of meaning used is $\alpha = 0.05$ on this research.

RESULTS AND DISCUSSION

The study results were analyzed through a special approach, with grading methods according to Avdagic research, such as in Table 1. By looking at the picture of kidney histopathology through a light microscope in the five treatment groups obtained the following picture

as shown in Figure 1. The five treatment groups that have been studied are made in the form of Table 2 analyzed through grading in Avdagic research in the following results in Table 2. The maximum results were seen in the chart of kidney tubular damage in all animal groups; try this study as follows in Figure 2.

Kruskal Wallis and Mann-Whitney U statistical analytics results

Based on the Kruskal-Wallis test, results obtained a p <0.03 value. Suppose used α=0.05 due to the p <α value. It can be concluded that there is a meaningful difference in kidney damage assessed based on the histopathological picture of renal tubular cells between the five groups. Post Hoc analysis is required to find out the differences between all group treatment.

The test to perform post hoc analysis for the Kruskal-Wallis test is with the Mann-Whitney test. In the Mann-Whitney test results, the degree of kidney damage between the standard feed treatment group and the streptozotocin-induced group of animals found a meaningful difference of degrees between the negative control group and the positive control group.

Mann-Whitney's test results showed kidney damage between the standard fed animal group and the group of animals given streptozotocin and then given golden sea cucumber extract (*Stichopus hermanii*) had an average meaningful difference between those groups.

Mann-Whitney's test results showed that kidney damage between a group of animals given streptozotocin and a group of animals given streptozotocin and then treated using gold extract showed meaningful difference results except at low doses of 4.25 mg/kg BW.

Analysis through the Kruskal-Wallis test was used to prove there was a significant difference in kidney damage assessed through histopathological descriptions of the group of animals given standard feed, group of animals tried that only induced streptozotocin, a group of animals tried with streptozotocin-induced and given golden sea cucumber extract (*Stichopus hermanii*) at a dose of 4.25 mg/kg BW, a group of animals tried with streptozotocin-induced and given golden sea cucumber extract (*Stichopus hermanii*) at a dose of 8.5 mg/kg BW. And groups of animals tried with streptozotocin-induced and given golden sea cucumber extract (*Stichopus hermanii*) at a dose of 12.75 mg/kg BW obtained a value of p <0.03. If used α=0.05 due to the p <α value, it can be concluded that there is a meaningful difference in

Table 1: Table of Cell Necrosis Grading through Avdagic Research.

Grade	Score	Rate of Change
0	1	Normal
1	2	Tubular epithelial necrosis and necrosis (<1% total renal tubules)
2	3	Tubular epithelial necrosis and necrosis (<1/2 total renal tubules)
3	4	Tubular epithelial necrosis and necrosis (>1/2 total renal tubules)
4	5	Complete or almost complete necrosis of proximal tubules

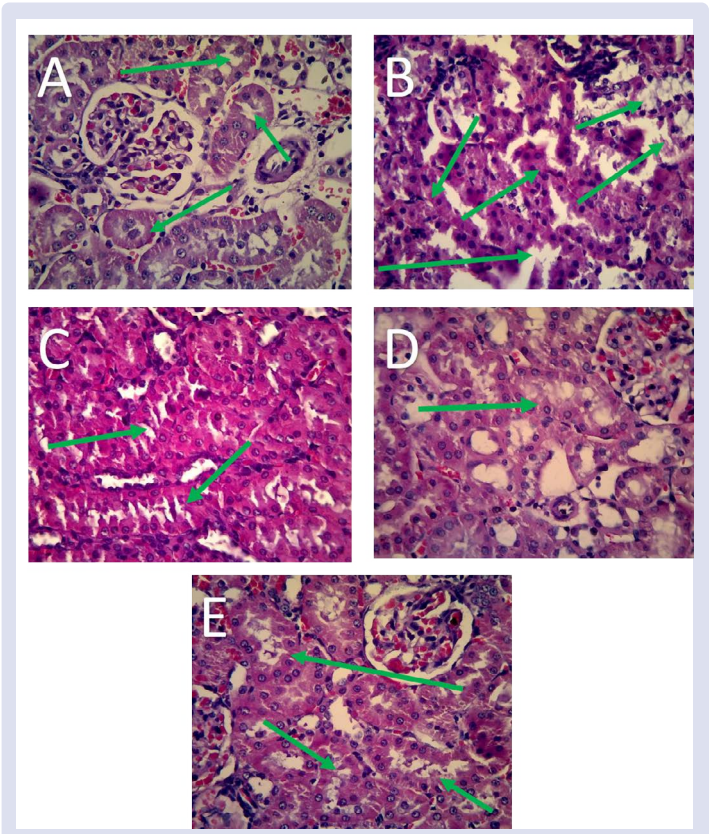


Figure 1: Overview of Renal Tubular Histopathology of All Groups of Animals. 1: Negative control, 2: Positive control, 3: Group 1, 4: Group 2, and 5: Group 3.

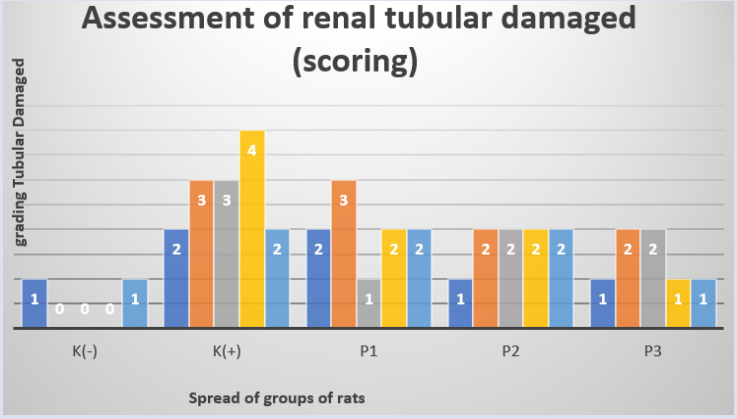


Figure 2: Kidney Tubular Damage Score Bar Diagram. K-: Negative control group Group of white rats (Rattus norvegicus) who were given standard feed and water had low degrees. K+: Histopathological assessment of renal tubular damage in rats in the STZ-induced positive control group with the lowest degree was two, and the highest degree was 4. P1: Histopathological assessment of kidney damage assessment of rat's treatment group 1 at a dose of 4.25 mg/kg BW and STZ-induced with the lowest degree was one, and the highest degree was 3. P2: Histopathological assessment results of kidney damage treatment group 2 at a dose of 8.5 mg/kg BW and STZ-induced with the lowest degree was one, and the highest degree was 2. P3: Histopathological assessment results of kidney damage treatment group 3 rats with a dose of 12.75 mg/kg BB and induced STZ with the lowest degree was one, and the highest degree was 2.

Table 2: Tubular Epithelial Damage Score Results.

Groups	No	Tubular Epithelial Damage					Mean
		I	II	III	IV	V	
Negative Control	1	1	1	0	1	0	1
	2	0	1	0	0	0	0
	3	0	1	0	0	0	0
	4	1	0	0	0	0	0
	5	0	0	1	1	1	1
Positive Control	6	2	2	3	2	3	2
	7	4	3	3	2	3	3
	8	2	3	3	2	3	3
	9	2	3	3	4	4	4
	10	3	3	2	3	4	2
P1	11	2	2	2	1	1	2
	12	3	3	2	3	2	3
	13	2	1	1	1	2	1
	14	0	3	2	2	3	2
	15	2	3	3	3	1	2
P2	16	0	1	2	3	1	1
	17	1	1	3	2	3	2
	18	2	2	3	2	1	2
	19	3	2	2	2	0	2
	20	1	2	1	2	2	2
P3	21	1	1	2	2	1	1
	22	1	1	2	2	2	2
	23	0	2	2	1	2	2
	24	1	1	2	1	2	1
	25	2	1	2	1	1	1

Description: P1: Treatment Group 1; P2: Treatment Group 2; P3: Treatment Group 3

kidney damage assessed based on the histopathological picture of renal tubular cells between the five groups.

Based on the results of the study, judging by the different histopathological picture between negative control and a positive control group that is a group of trial animals that only induced streptozotocin showed the result of a meaningful difference in the degree of kidney damage, seen through the histopathological picture of animals tried with a negative control group showed the intensity of necrosis cells due to the induction of streptozotocin doses of 40 mg/kg BW and 50 mg/kg BW multiple low dose rats. This corresponds to the research of streptozotocin-induced doses in rats (100 or 200 mg/kg BW) for 21 days already causing renal histological damage, especially mild glomerular necrosis and tubular atrophy.[20-22]

Streptozotocin is one of the agents that can be used to create experimental dialectical conditions in rats. The mechanism of Streptozotocin is its ability to cause toxic effects by penetrating pancreatic β cells through the glucose transporter GLUT 2; after penetrating pancreatic cells, DNA alkylation occurs through increased activity of the cyclase guanylyl and the formation of cGMP by STZ through the nitrosourea group resulting in damage to pancreatic β cells. Prolonged damage, resulting in the onset of high oxidative stress in the kidneys that eventually leads to lipid peroxidation in the endothelial cell membranes of glomerulus and tubules. This causes damage to glomerular endothelial cell membranes, resulting in decreased filtration function of the glomerulus. This condition causes serum urea and creatinine levels to increase.[19] Diabetic nephropathy is the most common microvascular complication that occurs in patients with DM and causes several abnormalities in the histological structure of the kidneys, namely changes in the glomerulus.[23]

Previous research has shown that gold sea cucumber extract (*Stichopus hermanii*) contains several active compounds, including Damaiyanti, which conducts research into the characterization of golden sea cucumber water and is detected to contain active compounds involved in the tissue healing process in the body, including amino acids, glycosaminoglycan, omega 3, saponins, and important elements such as zinc and calcium.[11]

The eleven amino acids in sea cucumbers that play a major role are eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), a tissue wound healing compound. The role of zinc content in wound healing also shows an increased response to zinc needs in cured tissues. Zinc works on the replication of fibroblasts, collagen synthesis, and collagen cross binding. Calcium in sea cucumbers has structural support, cell insulation, mitosis, blood coagulation, muscle contractions, and glandular secretions. Another role is to regulate the physiological body such as proliferation, signaling neurons, and contractions to be important in intracellular regulation. Glycosaminoglycans consist of several complex carbohydrate chains characterized by their amino sugar content and uric acids if the chain is attached to a protein molecule called a proteoglycan compound. Its properties hold large amounts of water and fill the space to become a lubricant such as glycosaminoglycans in hyaluronic acid, chondroitin sulfate, and heparin. The FGF (fibroblast growth factor) in glycosaminoglycans is angiogenic that accelerates wound healing. Saponins as an anti-microbial that will damage the cytoplasmic membrane and kill cells. Flavonoid compounds are suspected of denaturing microorganisms to prevent infection and spur collagen repair, thereby accelerating wound healing.[11,24] The absence of omega 3 is also important, which serves as an anti-inflammatory to increase procollagen.

CONCLUSION

In conclusion, administration of golden sea cucumber extract (*Stichopus hermanii*) at a dose of 12.75 mg/kg BW of rats for 21 days lowered the degree of tubular damage to the kidney rectus of white rats (*Rattus norvegicus*) male streptozotocin-induced strains.

ACKNOWLEDGMENT

We thank EJA, Indonesia for editing the manuscript.

We thank Universitas Hang Tuah, Indonesia for the financial support.

DISCLOSURE STATEMENT

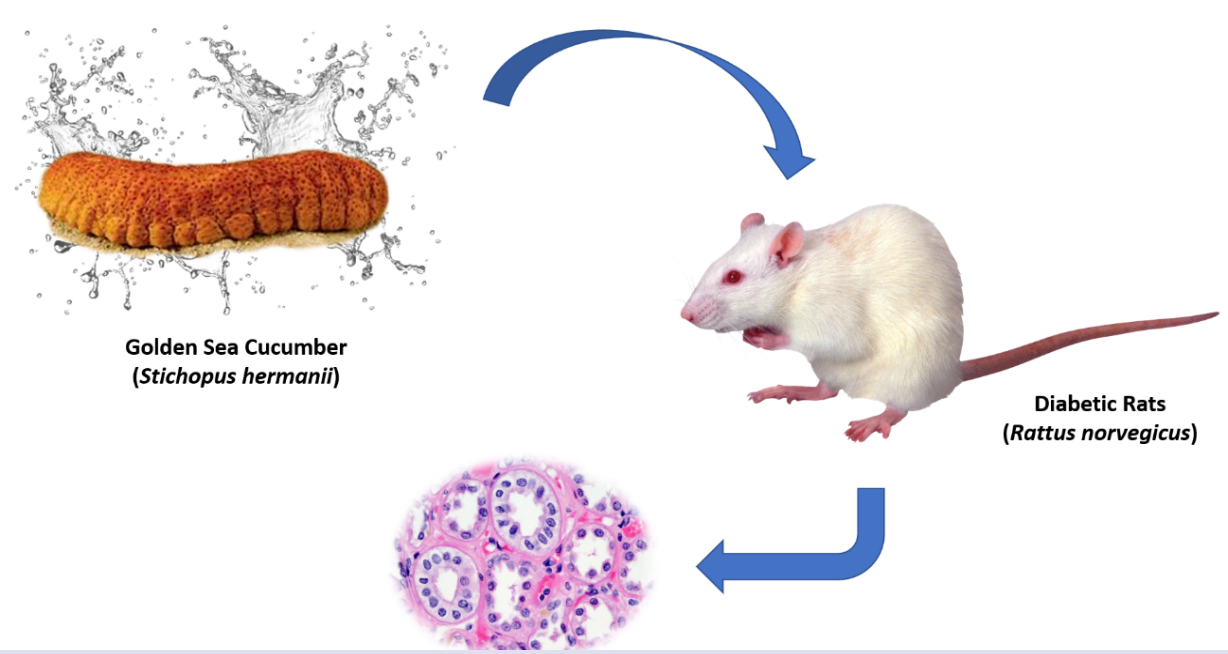
No conflicts of interest.

REFERENCES

1. Hayaza S, Istiqomah S, Susilo RJK, *et al*. Antidiabetic activity of ketapang (*Terminalia catappa* L.) leaves extract in streptozotocin-induced diabetic mice. Indian Vet J. 96(12): 11-13.
2. Tacharina MR, Ansori ANM, Plumeriastuti H, *et al*. Beneficial effect of grinting grass (*Cynodon dactylon*) on the streptozotocin induced diabetes mellitus in the mice. Indian Vet J. 97(4): 35-38.
3. Ansori ANM, Susilo RJK, Fadholly A, *et al*. Antidiabetes type 2 phytomedicine: mangosteen (*Garcinia mangostana* l.)-A review. Biochem Cell Arch. 20: 3173-3177.
4. Departemen Kementrian Kesehatan Republik Indonesia (2018). Riset kesehatan dasar (RISKESDAS). Goverment of Republic Indonesia link website in www.depkes.go.id/article/view/18121200001/prevent-prevent-and-prevent-the-voice-of-the-world-fight-Diabetes.html.
5. Rivandi J, Yonata A. Hubungan diabetes melitus dengan kejadian gagal ginjal kronik relationship between diabetic nephropathy and incident with chronic kidney disease. Majority. 2015; 4(9): 27.
6. Kementrian Kelautan dan Perikanan Republik Indonesia (2017). Maritim Indonesia, Kekayaan Kemewahan Luar Biasa Indonesia. http://www2.kkp.go.id/artikel/2233-maritim-indonesia-kemewahan-yang-luar-biasa.
7. Husen SA, Setyawan MF, Syadzha MF, *et al*. A novel therapeutic effects of *Sargassum ilicifolium* alginate and okra (*Abelmoschus esculentus*) pods extracts on open wound healing process in diabetic mice. Res J Pharm Tech. 13(6): 2764-2770.
8. Pusat Penelitian LIPI (2017). Teripang Indonesia: Eksplorasi, Pengelolaan dan Keterkaitannya Dengan oseanografi di perairan Indonesia, Pulau Biak, Provinsi Papua Indonesia. www.oseanografi.lipi.go.id/haspen/Teripang%20Biak.pdf.
9. Rasyid A, Wahyuningsih T, Ardiansyah A. Profile of Secondary Metabolites, Antibacterial Activity and Compound Composition in The Methanolic Extract of Sea Cucumber *Stichopus horrens*. Jurnal Ilmu dan Teknologi Kelautan Tropis. 10(2): 333-340. X
10. Bilgin Ş, Öztürk Tanrikulu H. The changes in chemical composition of Holothuria tubulosa (Gmelin, 1788) with ambient-drying and oven-drying methods. Food Sci Nutr. 2018; 6(6): 1456-1461.
11. Damaiyanti DW. Characterization of Water Extract Gold Sea Cucumber (*Stichopus hermanii*). Denta Jurnal Kedokteran Gigi. 2015; 9(1).
12. Pangestuti R, Arifin Z. Medicinal and health benefit effects of functional sea cucumbers. J Tradit Complement Med. 2017; 8(3): 341-351.
13. Safitri I, Purwanto B, Prabowo GI, et al. Effect of Sticophus hermanii extract on fasting blood glucose and skeletal muscle glut4 on type 2 diabetes mellitus rats model. IOP Conf Ser: Earth Environ Sci. 2019; 217: 012025.
14. Raza H, John A. Streptozotocin-induced cytotoxicity, oxidative stress and mitochondrial dysfunction in human hepatoma HepG2 cells. Int J Mol Sci. 2012; 13(5): 5751-5767.
15. Damasceno DC, Netto AO, Iessi IL, *et al*. Streptozotocin-induced diabetes models: pathophysiological mechanisms and fetal outcomes. Biomed Res Int. 2014; 2014: 819065.
16. Fitriyani A, Winarti L, Muslichah S, *et al*. Anti-inflammatory activity of *Piper crocatum* Ruiz & Pav. leaves metanolic extract in rats. Majalah Obat Tradisional. 2011; 16(1): 34-42.

17. Husen SA, Ansori ANM, Hayaza S, *et al*. Therapeutic effect of okra (*Abelmoschus esculentus* moench) pods extract on streptozotocin-induced type-2 diabetic mice. Res J Pharm Tech. 12(8): 3703-3708.
18. Avdagić N, Nakas-Ićindić E, Rasić S, *et al*. The effects of inducible nitric oxide synthase inhibitor L-N6-(1-iminoethyl) lysine in gentamicin-induced acute tubular necrosis in rats. Bosn J Basic Med Sci. 2007; 7(4): 345-351.
19. Robbins. 'Robbins' Pathologic Basis of Disease 9th edition'. Journal of Clinical Pathology. 2013.
20. Husen SA, Wahyuningsih SPA, Ansori ANM, *et al*. The effect of okra (*Abelmoschus esculentus* moench) pods extract on malondialdehyde and cholesterol level in stz-induced diabetic mice. Eco Env Cons. 25(4): S50-S56.
21. Ansori ANM, Susilo RJK, Hayaza S, *et al*. Renoprotection by *Garcinia mangostana* L. pericarp extract in streptozotocin-induced diabetic mice. Iraqi J Vet Sci. 33(1): 13-19.
22. Husen SA, Salamun, Ansori ANM, *et al*. Renal protective effects of gamma-mangostin in streptozotocin-induced diabetic mice. Indian J Forensic Med Toxicol. 13(3): 1221-1226.
23. Khotimchenko Y. Pharmacological potential of sea cucumbers. Int J Mol Sci. 2018; 19(5): 1342.
24. Ansori AN, Fadholly A, Proboningrat A, *et al*. Novel antiviral investigation of *Annona squamosa* leaf extract against the dengue virus type-2: *In vitro* study. Phcog J. 2021; 13(2): 456-462.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Herin Setianingsih. Lectures and researcher at the Faculty of Medicine Universitas Hang Tuah Surabaya Indonesia. She had been awarded her Doctoral program from Universitas Airlangga Surabaya Indonesia. The research Interest: Anti-diabetic, Hyperlipidemia, Cardiovascular action, Anti-inflammatory, Anti-Viral, Marine natural product, COVID-19, Hyperbaric Oxygen Therapy and all about molecular biology.

Satria Erda Wisnumarta. He is a graduate student in medicine at the Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia. he graduated with a medical degree in 2020 and is still continuing his doctoral program.

Sareh Arjono Tjandra. Graduated from the Medical Faculty of Airlangga University in 1973. He is a senior lecturer in clinical pathology at the Faculty of Medicine, Universitas Hang Tuah, Surabaya, Indonesia.

Cite this article: Setianingsih H, Wisnumarta SE, Tjandra SA. Repairing of Renal Tubules in Diabetic Rats (*Rattus norvegicus*) Diabetes After Administration of Golden Sea Cucumber (*Stichopus hermanii*). Pharmacog J. 2021;13(4): 958-964.