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ARTICLE

THE EFFECT OF ETHANOL EXTRACT OF GOLDEN SEA CUCUMBER (*Stichopus hermanii*) ON ALT LEVELS IN ASPIRIN-INDUCED WISTAR MALE RATS (*Rattus norvegicus*)

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ABSTRACT

In the US and Europe, drug-induced liver injury is the leading cause of acute liver failure, killing 10%–50% of patients. Free radicals from high aspirin doses or extended use can damage hepatocytes. Natural antioxidants include glycine, glutamic acid, and flavonoid in golden sea cucumber (Stichopus hermanii) help fight free radicals. This study will examine how Stichopus hermanii extract affects ALT levels in aspirin-induced Rattus norvegicus. In a post-test only control group design, 32 wistar male rats were separated into four groups: negative control (K-), positive control (K+), and two groups treated with Stichopus hermanii extract at 486 mg/kg BB (KP1) and 972 mg/kg BB (KP2) for 23 days. In the Man-Whitney test, neither the 486 mg/kg BB nor 972 mg/kg BB groups demonstrated a significant reduction in ALT levels compared to positive control. ALT levels were similar amongst extract dosages. This study found that aspirin-induced animals who received Stichopus hermanii extract at 486 mg/kg BB and 972 mg/kg BB for 23 days had no ALT reduction.

Keywords: *Stichopus hermanii*; ALT; Drug-Induced Liver Injury; Flavonoid; Glycine; Glutamic acid

АБСТРАКТ

В США и Европе лекарственное поражение печени является основной причиной острой печеночной недостаточности, от которой умирает 10–50 % пациентов. Свободные радикалы, образующиеся при приеме высоких доз аспирина или длительном его применении, могут повреждать гепатоциты. Натуральные антиоксиданты, в том числе глицин, глутаминовая кислота и флавоноиды, содержащиеся в золотом морском огурце (Stichopus hermanii), помогают бороться со свободными радикалами. В данном исследовании будет изучено влияние экстракта Stichopus hermanii на уровень АЛТ у крыс Rattus norvegicus, которым вводился аспирин. В контрольной группе, прошедшей только пост-тестирование, 32 самца крыс породы Вистар были разделены на четыре группы: отрицательный контроль (K-), положительный контроль (K+) и две группы, получавшие экстракт Stichopus hermanii в дозе 486 мг/кг массы тела (KP1) и 972 мг/кг массы тела (KP2) в течение 23 дней. В тесте Манна-Уитни ни группа с дозой 486 мг/кг массы тела, ни группа с дозой 972 мг/кг массы тела не продемонстрировали значительного снижения уровня АЛТ по сравнению с положительным контролем. Уровни АЛТ были схожими при всех дозах экстракта. Это исследование показало, что у животных с аспирин-индуцированным воспалением, которые получали экстракт Stichopus hermanii в дозе 486 мг/кг массы тела и 972 мг/кг массы тела в течение 23 дней, не наблюдалось снижения уровня АЛТ.

Ключевые слова: *Stichopus hermanii* ; АЛТ; Лекарственно-индуцированное поражение печени; флавоноид; Глицин; Глутаминовая кислот

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INTRODUCTION

Drug-Induced Liver Injury (DILI) is a toxic drug reaction that results in liver injury. Drug-induced liver injury is the most common cause of acute liver failure in the United States and Europe. The case fatality rate of DILI is 10-50%. DILI occurs at an annual incidence of approximately 14-19 per 100,000 population in France and Iceland. Such potentially fatal events have an important impact on policy making in tightening drug restrictions.[1,2]

Aspirin or *acetylsalicylic acid* is a non-steroidal anti-inflammatory drug (NSAIDs) that reduces inflammatory symptoms and has various pharmacological effects including antipyretic, analgesic, and antiplatelet. Aspirin use is associated with severe morbidity and mortality due to its adverse effects on several organs, including the liver, stomach, and kidneys. One of the consequences of long-term aspirin use is hepatotoxicity.[3] Hepatic toxicity is influenced by the dose of aspirin taken and the duration of administration.

Hepatic damage can occur due to aspirin administration beyond the therapeutic dose. Hepar is a very vulnerable organ to drug toxicity, so to monitor hepatic damage, specific hepatotoxic indicators such as ALT are measured [4]. ALT is one of the enzymes in the human body as a marker of impaired hepatic function. ALT is found in several organs of the human body, such as the liver, heart muscle, kidneys, and skeletal muscle.[5]

Indonesia has a diversity of marine biota that can be utilized as raw materials for alternative medicine, one of which is sea

cucumber. Sea cucumbers are marine invertebrates that have been used for food, traditional medicine, and cosmetics. Sea cucumbers also have the potential for antioxidants, anti-inflammatory, antidiabetic, anti-obesity, and antimicrobial. Sea cucumbers have high commercial value in Indonesia and high economic value in Asian markets. One type of sea cucumber in Indonesia that has a high selling value is *Stichopus hermanii*. Golden sea cucumber (*Stichopus hermanii*) is included in the genus Stichopus which contains quite complete amino acids such as glycin and glutamic acid which can play a role in helping increase GSH synthesis.[6,7] The flavonoid content contained in *Stichopus hermanii* also has antioxidant abilities in inhibiting the formation of free radicals, so it can act as a hepatoprotector.[8]

This study aims to examine the effect of giving golden sea cucumber extract (*Stichopus hermanii*) as a hepatoprotector in aspirin-induced experimental animals, with the parameter of ALT levels as a marker of hepatic damage.

MATERIAL AND METHODS

A series of animal studies were conducted at the Integrated Biomolecular and Hyperbaric Laboratory, Faculty of Medicine, Hang Tuah University, Surabaya, No. I/053/UHT.KEPK.03/VIII/2024.

A genuine experimental design that featured a post-test only control group was the study design that was employed. The animals employed in this investigation were 32 white male rats belonging to the Rattus norvegicus species and the Wistar strain. The rats were between 3 and 4 months old and had a body weight of 150 to 200 grams. The sample size calculation that was employed in this investigation was the Federer formula. The rats were divided into 4 treatment groups, as follows:

1. Negative control group is a group of 6 rats were given standard feed and drink for 23 days.
2. Positive control group is a group of 6 rats were given food, drink, and aspirin dose of 250 mg/kg BW on 13th day to 23rd day
3. First treatment group: a group of 6 rats were given standard feed, drink, *Stichopus hermanii* extract at a dose of 486 mg/kg BW for 23 days, then given aspirin at a dose of 250 mg/kg BW starting on 13th day of sea cucumber administration for 11 days.

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4. Second treatment group: a group of 6 rats were given standard feed, drink, *Stichopus hermanii* extract dose of 972 mg/kg BW for 23 days, then given aspirin dose of 250 mg/kg BW starting on the 13th day of administration of sea cucumber for 11 days.

In this study, there were 7 days of acclimatization period and 23 days of treatment period, so that blood serum collection used for ALT examination was carried out on day 31.

The tools used in this research are animal cages with a size of 40 cm x 30 cm x 10 cm, husk, handschoen, feeding and drinking utensils for experimental animals, scales to measure the body weight of the rats, sonde for administering *Stichopus hermanii* extract, micropippet uk 10-100 µl labnet, uk 20-200 µl, uk 100-1000 µl, centrifuge tube 10 ml RRC, spectrofotometer bio-rad smartspec™ plus, vortex – wiggens, sentrifuse hermle Z 207 A, aluminium tube rack, yellow tips, blue tips, Oven – binder**,** Rotavapor – biobase**,** Pompa vacum medi-pump-thomas**,** Oil bath – biobase**,** accuris analytical scales**,** Waterbath – polyscience**,** Erlenmayer 1000 and 2000 ml pyrex.

The materials used in this research are white rats (*Rattus norvegicus*) wistar strain male as many as 32 animals, feeding and drinking water, *Stichopus hermanii* extract dose of 486 mg/kg BW and 972 mg/kg BW, aquadest, 96% ethanol, aspirin dose of 250 mg/kg BW, ketamine 40-80 mg / kg BB.

Preparation of extract *Stichopus hermanii*

Approximately 6 kg of golden sea cucumbers were harvested from Sabunten Island in the district of Sapeken, in the regency of Sumenep. At the Department of Biology, Sepuluh November Institute of Technology, a series of taxonomic tests were conducted in order to ensure that the species in question was, in fact, the golden sea cucumber (Stichopus hermanii). The preparation of golden sea cucumber (Stichopus hermanii) extract was carried out based on references [9,10]as follows:

1. Gold sea cucumber that has been cleaned and taken inside, then cut about 3-10 cm.
2. The golden sea cucumber is oven dried and then blended into powder.
3. The sea cucumber powder was macerated and stirred repeatedly for about 8 hours.
4. The gold sea cucumber powder was soaked in 96% ethanol solution for 24 hours. The 96% ethanol solution was collected and the golden sea cucumber pulp was remacerated with 96% ethanol in the same way.
5. The remaceration result will be evaporated at 45-50°C water temperature and the gold sea cucumber extract will be produced.

Preparation of aspirin solution

Aspirin solution was prepared using aspirin tablets branded "Cardio Aspirin" which was given by round with a dose of 250 mg/kg BW. Calculation of aspirin in rats with average body weight, as follows: 50 mg / 200 g BW given for 11 consecutive days.

Aspirin was suspended using 1% CMC-Na solution.[11] The solution was stirred with unidirectional rotation and constant speed until homogeneous.

Preparation of CMC-Na 1% solution

CMC-Na 1% solution was made with 1 gram and dissolved into 100 ml of distilled water. The solution was stirred until homogeneous and evenly distributed.[12]

Method of blood anesthesia

Ketamine anesthesia was performed on the 23rd day after the treatment period, for the examination of ALT levels. The dose of ketamine used was approximately 40-80 mg/kg BW intramuscularly.[13]

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Anesthesia was performed in the following manner:

1. The rat is held by grasping the neck and fixed with the help of another person.
2. Ketamine injection is done on the thigh of the rat.
3. The rat is checked for foot reflexes to ensure pain reflexes.

Method of blood collection

White rats (*Rattus norvegicus*) that have been given anesthesia, blood is taken intracardially approximately 5 ml, in the following manner:

1. Rats were placed on a surgical mat in a supine position after anesthesia.
2. The rat is palpated in the area of the beating heart.
3. The rat are dissected using scissors by opening the skin until the muscle from the epigastric region to the heart is visible.
4. Blood collection of 5 ml was done with a 5 cc syringe.
5. Blood was transferred into EDTA, then placed into a test tube to be processed for ALT examination.

Examination of hepatic ALT levels

Utilizing the Chemistry Autoanalyzer Cobas Integra 14, the International Federation of Clinical Chemistry (IFFC) kinetic technique was used to assess the ALT enzyme activity of rats (Rattus norvegicus). Blood that had been centrifuged was the source of the serum that was utilized for the ALT analysis.

Data Analysis

This study uses statistical tests that are processed using *Statistical Package for the Social Sciences* (SPSS) version 27.

RESULT

Results of ALT level examination

The average results of ALT levels in this study can be seen in Figure 1

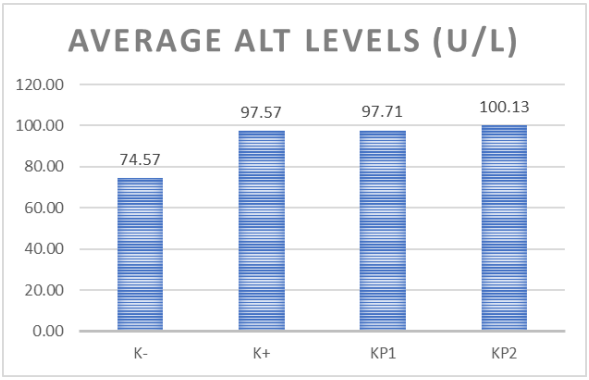

Figure 1. The average ALT levels in all groups

The findings in the table and graphic above indicate that the positive control group of rats exhibits elevated alanine transaminase (ALT) levels in comparison to the negative control group. There was no significant decrease in ALT levels in the KP1 and KP2 groups when compared to the positive control group. The purpose of this test is to investigate whether or not the acquired data follows a normal distribution. The Shapiro-Wilk test is the type of test of normality that is employed. This test is chosen if the number of samples used is less than 50. The results of the Shapiro-Wilk normality test in each group, as follows:

Table 1. The Results of normality test for ALT levels

Group		Shapiro-Wilk		
		Statistics	df	Sig.
ALT levels	K (-)	0.923	7	0.492*
	K (+)	0.894	7	0.297*
	KP1	0.754	7	0.014
	KP2	0.941	8	0.619*

Note : * means significance p > 0.05, then the data is normally distributed

According to the findings of the Shapiro-Wilk normality test, which are presented in table 1, normally distributed data with a p value greater than 0.05 are found in the negative group (p = 0.492), the positive group (p = 0.297), and treatment group 2 (p = 0.619). With a significance value of 0.014, the KP1 group was the one that did not have a distribution that was considered typical.

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Table 2. The results of non-parametric (*Kruskal-Wallis*) test for ALT levels

Test Statistics	
	SGPT
Kruskal-Wallis H	9.452
df	3
Asymp. Sig.	0.024*

Note : *means p < 0.05, so there is a significant difference

The results of the Kruskal-Wallis test in table 2 showed a significant result of 0.024 which means that there is a difference in the average ALT levels in animals that have been given treatment.

Table 3. The results of post hoc test (*Mann-Whitney U*) test for ALT levels

	K (-)	K (+)	KP1	KP2
K (-)		0.018*	0.005*	0.028*
K (+)			0.482	0.728
KP1				0.451

Note : * means p < 0.05, so there is a significant difference

The difference is between K- and K+ with a value of 0.018, K- with KP1 with a value of 0.005, K- and KP2 with a value of 0.028. K+ with KP1 with a value of 0.482, K+ with KP2 with a value of 0.728, KP1 with KP2 with a value of 0.451. Based on the data in table 3, it can be concluded that each group has not significant differences in ALT levels.

DISCUSSION

Based on the results of research on rat ALT, the criteria that meet the inclusion were 29 rats. During the study there were 3 experimental animals that fell into the drop out criteria, namely 1 from the negative control group (-), 1 from the control group (+), and 1 from the KP1 group. Death in rats is most likely caused by stress. Based on[15], stressors that trigger death are caused by several environmental factors, such as:

1. Inadequate circulation aspects can cause particulate contaminants such as allergens and pathogens in the air, so it is necessary to provide sufficient ventilation to provide good air quality and oxygen supply.
2. Temperatures that are above normal can cause dehydration in rats, potentially leading to death.
3. Lighting can affect physiological, morphological and behavioral aspects of various animals. Potential stressors from light include photoperiod, light intensity and inappropriate spectral quality of light.
4. Cleaning chaff less than twice a week has the potential to cause disease-causing microorganisms in rats.

Deaths in rats can also be caused by fighting among male rats that live together in groups. About 14% of male rats that fight have skin injuries that have the potential for bleeding and death.[16]

Aspirin is a class of NSAIDs that has the potential to cause poisoning and is hepatotoxic when used in large quantities and for a long time.[17] Hepatotoxicity caused by drugs is a very risky clinical problem and affects liver metabolism.[18] High doses of aspirin are metabolized through hepatic conjugation to form salicylate interactions. Disposal of metabolic waste substances that are toxic is very necessary, if not removed it can cause disruption of the function of organs in the body. Drugs used that are not in accordance with the indication, dose, and duration of administration will cause pathophysiology, including due to aspirin.[19]

High concentrations of salicylate will be carried to the liver through the hepatic portal vein. The vein is the site used for absorption and first metabolism in the liver. Aspirin is rapidly metabolized with the help of esterase enzymes into salicylic acid and p450 to form

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metabolites such as gentisate. This metabolite is formed by hepatocyte mitochondria, causing an interaction between salicylate and hepatic mitochondria.[20]

Excessive use of aspirin will cause salicylate uptake in the liver which has the potential for mitochondrial damage. Mitochondrial damage can affect fatty acid metabolism through competitive inhibition of long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) enzyme involved in fatty acid β-oxidation.[21]

Hepatocytes require fatty acids through oxidative phosphorylation of the tricarboxylic acid cycle in mitochondria to produce energy. In the respiration chain, electrons are transferred from NADH or FADH2 to oxygen molecules, causing the reduction of oxygen to H2O. Some oxygen molecules that experience incomplete reduction will produce a by-product in the form of superoxide (O2-). The respiration chain that occurs in the mitochondria produces superoxide (O2-) as a by-product that will react with iron-sulfur and produce Fe2+ ions. The presence of Fe2+ ions and hydrogen peroxide causes the formation of reactive hydroxy radicals (OH-). The superoxide can also react with nitric oxide (NO-) to form peroxynitrite (ONOO-). These two species (OH- and ONOO) can trigger oxidative stress that leads to hepatocyte cell damage.[22] Hepatocytes will fail to maintain their intracellular activity, if there is no ATP generated through the utilization of fatty acids.

This study used a dose of aspirin 250 mg/kg BW for 11 days which can trigger damage to liver cells. Damage to the liver will cause liver enzymes to escape into the bloodstream, so that blood levels increase and indicate impaired liver function[23]. This research is in line with research conducted by Al-Bidhani in 2021 that the administration of aspirin at a dose of 100mg / kg BW to male rats (*Rattus norvegicus*) for periods of 10 days, 20 days, and 30 days is also able to cause liver damage and increase ALT levels.[24]

ALT will catalyze the transfer of amino groups from L-alanine to alpha-ketoglutarate, and the conversion products are L-glutamate and pyruvate through the tricarboxylic acid (TCA) cycle. Pyruvate can be used in the citric acid cycle to generate ATP. Pyridoxysal 5'-phosphate, also known as vitamin B6, is a coenzyme required in this reaction. Pyridoxal 5'-phosphate (P-5′-P) belongs to the prosthetic group that binds to the inactive apoenzyme. The pyridoxal 5'-phosphate attached to the apoenzyme will accept an amino group from the first substrate i.e. aspartate or alanine and produce products such as oxaloacetate or pyruvate. The coenzyme in amino form then transfers the amino group to 2-oxoglutarate as the second substrate to form glutamate. Coenzyme-deficient apoenzymes and holoenzymes are usually present in serum, so adding P-5′-P can increase aminotransferase activity.[25]

Elevated ALT levels are a biomarker in hepatic damage because they are found in the liver, especially the cytosol. Glutamic oxaloacetic transaminase is required by the body in the transaminase process to reduce excess ammonia. This enzyme is more specifically found in the heart, muscles, pancreas, lungs, and skeletal muscles.[26]

Hepatic cell damage can trigger oxidative stress caused by increased levels of free radicals in the body. These radicals tend to hold a chain reaction that if it occurs in the body will be able to cause damage that continues and continues, so the body needs additional antioxidants from outside that can protect against free radical attacks [27]This is similar to research conducted by Fadlilah and Lestari in 2023 that adequate antioxidants can prevent the harmful effects of reactive oxygen species (ROS) production and immune cell damage. Antioxidants are necessary in regulating reactions that release free radicals.[28]

Active substances from marine life that have pharmacological activity in recent years, including Stichopus hermanii. This type of sea cucumber contains many antioxidants that can counteract free radicals, so it has the potential

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as a hepatoprotector. Golden sea cucumber (Stichopus hermanii) has content that has the potential to increase GSH in the form of amino acids such as glycin and glutamic acid. GSH functions as an antioxidant defense by reduction of oxidative stress and maintenance of redox balance, metabolic detoxification of xenobiotics, and modulation of the immune system. GSH will scavenge various oxidant molecules, such as superoxide anion, hydroxyl radical, nitric oxide, and carbon radical. *Stichopus hermanii* plays a role in providing precursors, cofactors, and certain nutrients to increase or maintain optimal glutathione levels.[29]

Stichopus hermanii also contains alkaloid, flavonoid, phenol, saponin, and terpenoid compounds. These secondary metabolite compounds have bioactivity as antibacterial, antifungal, and antioxidant. The content of metabolite compounds that function as hepatoprotectors is flavonoids.[30]

Flavonoids are compounds found in natural materials with broad pharmacological and therapeutic significance. The effectiveness of flavonoids depends on absorption, distribution, metabolism, and excretion. The therapeutic potential in various types of flavonoids can address human diseases, including liver injury. Excessive production of ROS can limit the antioxidant ability of hepatocytes, decrease various cell signaling pathways, and promote cell death through the process of apoptosis. Flavonoids have antioxidant properties, thus exerting hepatoprotective effects mainly by ameliorating oxidative stress, inflammation, and regulation of lipid metabolism.[31]

Research on the administration of golden sea cucumber extract (Stichopus hermanii) at a dose of 486mg / kg BW and 972mg / kg BW for 23 days, as well as the administration of aspirin at a dose of 250mg / kg BW for 11 days was not proven as a hepatoprotector with the results of ALT levels that did not show a significant decrease compared to the group that was only induced with aspirin. This could be due to several other factors, such as:

1. Long-term storage of sea cucumber using freezing process for 8 days at 4ºC can drastically reduce the elasticity. This decrease can affect the quality and degradation of tissue proteins in sea cucumbers. Sea cucumber tissue can survive intact for up to five days. On day 7, protein degradation occurs due to tissue necrosis in sea cucumbers during the storage process.[32] During the freezing process of marine products, ice crystal growth and protein denaturation will induce protein oxidation, thus causing changes in physical and chemical properties, functional properties, and nutritional quality. Improving the quality of seafood can be done by paying attention to effective packaging methods, exploring the molecular interactions of protein oxidation products, and applying new analytical techniques to dig deeper into the degree of protein oxidation to amino acids.[33]
2. The thawing method performed prior to the preparation of liquid extracts on frozen sea cucumbers has an impact on the microstructure of the sea cucumbers. Damage to the microstructure during the thawing process can lead to changes in moisture migration and protein oxidation. [34] Thawing methods can cause loss of nutritional value, lipid and protein oxidation, and microbial reproduction, so it needs to be explored to obtain better quality sea cucumbers.[35]
3. The use of too high a temperature during the extraction process can potentially remove some of the metabolites contained in sea cucumbers. This can also cause degradation of constituents contained in liquid extracts, so it is recommended to use temperatures around 30-40ºC so that the bioactive compounds in sea cucumbers are maintained.[36,37] Extraction temperatures that are too high cause

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damage to compounds due to the oxidation process. Flavonoid components can produce low quality, if the extraction process is carried out at high temperatures. [38]

4. This study used 96% ethanol solvent in extracting *Stichopus hermanii* because it is selective, non-toxic, good absorption, and high filtering ability on polar compounds. This solvent can produce more concentrated extracts compared to solvents with low concentrations.[39] Other studies explain that the higher the concentration of ethanol, the lower the level of polarity. The use of ethanol solvents with concentrations above 70% results in a decrease in total flavonoid levels, making it less effective in dissolving compounds that have low molecular weight. Different ethanol concentrations can affect the solubility of flavonoid compounds, therefore a more appropriate solvent selection is needed in the *Stichopus hermanii* extraction process.[40]
5. Repeated handling and rounding can cause physical stress. The stimulus will activate the amygdala to respond to threats and fear to the animal's vigilance.[41] Stressed animals can increase the secretion of ACTH (adenocorticotropic) which triggers the release of glucocorticoid hormones. These hormones increase metabolic processes through the process of gluconeogenesis. The process of gluconeogenesis converts fatty acids and amino acids into glucose. Stressful situations require more energy. The enzyme needed in the process of gluconeogenesis includes ALT. This enzyme will catalyze chemical reactions in hepatocyte cells, so increased hepatic performance can cause hepatocyte damage.[17]
6. Habitat differences can affect the metabolite content found in sea cucumbers. The content of secondary metabolites in an organism is influenced by several factors, one of which is environmental factors. This is due to differences in temperature, oxygen solubility, pH, salinity and light intensity. The results of the identification of secondary metabolites show that Holothuria atra extract from Lampung Bay Waters contains secondary metabolites, such as alkaloids, flavonoids, steroids and saponins, while Holothuria atra extract from Garut Waters contains secondary metabolites of alkaloids, flavonoids, steroids and triterpenes and saponins.[42]
7. Technology in Indonesia until now has not been able to extract only 1 metabolite compound, while *Stichopus hermanii* contains other secondary metabolites, such as saponins and alkaloids. These ingredients have the potential to cause cell damage. Saponins can cause hepatocyte cell disorders through erythrocyte hemolysis. Alkaloid content has toxic properties because it takes a long time in the process of metabolism and excretion, so that alkaloid contact becomes longer and damages hepatocyte cells.[43]Another study also explained that high concentrations of phenolic activity can turn into prooxidants.[44] Prooxidants are chemicals that induce oxidative stress through the formation of ROS by inhibiting the antioxidant system. Flavonoids can react as prooxidants when reduced to metals, but this depends on environmental conditions.[45]

CONCLUSION

The administration of golden sea cucumber extract (*Stichopus hermanii*) at a dose of 486mg / kg BW does not affect the ALT levels of white rats (*Rattus norvegicus*) wistar strain induced by aspirin. The administration of golden sea cucumber extract (*Stichopus hermanii*) at a dose of 972mg / kg BW does not affect the ALT levels of white rats (*Rattus norvegicus*) wistar strains induced by aspirin.

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DECLARATIONS

D.H.M.F contributed to the study design, data analysis and interpretation, and final review of the manuscript. D.P has read and approved the final manuscript. In addition, W.D and E.P played a role in writing and editing the article. This study has received ethical approval from the Health Research Ethics Commission, Faculty of Medicine, Hang Tuah University, Surabaya.

REFERENCES

1. Kullak-Ublick GA, Andrade RJ, Merz M, End P, Benesic A, Gerbes AL, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut. 2017 Jun;66(6):1154–64. https://doi.org/10.1136/Gutjnl-2016-313369.
2. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. Vol. 16, Therapeutic Advances in Gastroenterology. SAGE Publications Ltd; 2023. https://doi.org/10.1177/17562848231163410.
3. El-Sheikh SMA, Bahaa HM, Galal AAA, Metwally MMM, Said MA, Alattar RH, et al. Gastroprotective, hepatoprotective, and nephroprotective effects of thymol against the adverse effects of acetylsalicylic acid in rats: Biochemical and histopathological studies. Saudi J Biol Sci. 2022 Jun 1;29(6). https://Doi.Org/10.1016/J.Sjbs.2022.103 289.
4. Umoren EB, Okon IA, Modo EU, Etim OE, Brown PI, Owu DU, et al. Jatropha tanjorensis Euphorbiaceae ameliorates aspirin-induced hepatotoxicity and maintain electrolytes balance in albino Wistar rats. Phytomedicine Plus. 2023 May 1;3(2). https://doi.org/10.1016/J.Phyplu.2023.100450.
5. Sukmayanti NLPA, Artini NPR, Widayanti NP. Analisis Kadar SGPT (Serum Glutamic PyruvicTransaminase) Dan Kholinesterase Pada Petani Sayur Di Desa Riang Gede, Kecamatan Penebel, Kabupaten Tabanan. The Journal Of Muhammadiyah Medical Laboratory Technologist. 2020 Nov;3(2):25–31. https://doi.org/10.30651/jmlt.v3i2.5841.
6. Hossain A, Dave D, Shahidi F. Antioxidant Potential of Sea Cucumbers and Their Beneficial Effects on Human Health. Vol. 20, Marine Drugs. MDPI; 2022. https://doi.org/10.3390/Md20080521.
7. Gianto, Suhandana M, Putri RMS. Komposisi Kandungan Asam Amino Pada Teripang Emas (Stichoupus horens) di Perairan Pulau Bintan, Kepulauan Riau. Jurnal Teknologi Hasil Perikanan. 2017;6(2):186–92. https://doi.org/10.36706/FISHTECH.V6I2.5850.
8. Ayu I, Widiasriani P, Nyoman N, Udayani W, Afriyanchika G, Triansyah P, et al. Artikel Review: Peran Antioksidan Flavonoid dalam Menghambat Radikal Bebas. Journal Syifa Sciences and Clinical Research (JSSCR). 2024;6(2). https://doi.org/10.37311/Jsscr.V6i2.27055.
9. Yatmasari E, Setianingsih H. Potensi Teripang Emas (Stichopus hermanii) Terhadap Perubahan Histopatologi Hati Pada Tikus Dengan Induksi Streptozotocin. Vol. 1, Surabaya Biomedical Journal. 2021. https://doi.org/10.30649/sbj.v1i1.6
10. Rusmini R, Taurina W, Andrie M. Standardization of Golden Sea Cucumber (Stichopus hermanii) Extracts from Pelapis Island, Kayong Regency, West Kalimantan. Biology, Medicine, & Natural

Product Chemistry. 2023 Sep 20;12(2):539–45. https://doi.Org/10.14421/Biomedich.20 23.122.539-545.
11. Bele AJL. Histopathological Overview of Kidney Given Extract of Thistle Leaf (Calotropis gigantea) and Aspirin Inducted to White Rats (Rattus norvegicus). Journal of Basic Medical Veterinary Bele et al Desember [Internet]. 2022 Dec;11(2):64–74. Available from: https://e-journal.unair.ac.id/JBMV
12. Muljono P, Fatimawali, Manampiring AE. Uji aktivitas antibakteri ekstrak daun mayana jantan (Coleus atropurpureus Benth) terhadap pertumbuhan bakteri Streptococcus Sp. dan Pseudomonas Sp. Jurnal e-Biomedik. 2016 Jun;(1):164–72. https://doi.org/10.35790/ebm.v4i1.10860.
13. Siriarchavatana P, Ayers JD, Kendall L V. Anesthetic Activity of Alfaxalone Compared with Ketamine in Mice. Journal of the American Association of Laboratory Animal Science . 2016 Jul;55(4):426–30. https://pmc.ncbi.nlm.nih.gov/articles/PMC4943613/.
14. Permana IGPBT, Handajani F, Taruna D, Untari NKSD. Efek Pemberian Eucheuma spinosum sebagai Profilaksis dalam. Hang Tuah Medical Journal [Internet]. 2023;21(1). Available from: www.journal-medical.hangtuah.ac.id
15. Mutiarahmi CN, Hartady T, Lesmana R. Use Of Mice As Experimental Animals In Laboratories That Refer To The Principles Of Animal Welfare: A Literature Review. Indonesia Medicus Veterinus. 2021 Jan 31;10(1):134–45. https://doi.org/10.19087/Imv.2020.10.1. 134.
16. Theil JH, Ahloy-Dallaire J, Weber EM, Gaskill BN, Pritchett-Corning KR, Felt SA, et al. The epidemiology of fighting in group-housed laboratory mice. Sci Rep. 2020 Oct 6;10(1):16649. https://doi.org/10.1038/S41598-02073620-0.
17. Hayong NJ, Laut MM, Pandarangga P. Efek ekstrak etanol daun mimba (Azadirachta indica) terhadap kadar serum glutamat piruvate transminase (sgpt) dan gambaran histopatologi hepar pada mencit (Mus musculus) model hepatotoksik. Jurnal Veteriner Nusantara. 2019 Aug 1;2(2):141–52. https://ejurnal.undana.ac.id/jvn/issue/view/168.
18. Robiyanto R, Liana J, Purwanti NU. Kejadian Obat-Obatan Penginduksi Kerusakan Liver pada Pasien Sirosis Rawat Inap di RSUD Dokter Soedarso Kalimantan Barat. Jurnal Sains Farmasi & Klinis. 2019 Dec 30;6(3):274. https://doi.Org/10.25077/Jsfk.6.3.274285.2019.
19. Fathuridha I, Nailufar Y. Kajian Literatur Gambaran Histopatologis Organ Sistem Ekskresi Tikus Putih (Rattus Norvegicus) Yang Diinduksi Aspirin. 2020 Nov 14;1–16. http://digilib.unisayogya.ac.id/.
20. Bojić M, Sedgeman CA, Nagy LD, Guengerich FP. Aromatic hydroxylation of salicylic acid and aspirin by human cytochromes P450. European Journal of Pharmaceutical Sciences. 2015 Jun;73:49–56. https://Doi.Org/10.1016/J.Ejps.2015.03.015.
21. Prasun P, LoPiccolo MK, Ginevic I. Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency. Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. 2022 Sep 1 [cited 2024 Sep 27]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK583531/
22. Utami AR, Sitompul DT, Thomas F. Artikel Review : Stres Oksidatif dan Penyakitnya. 2023 Jan 6;1–44. Available from:

https://www.researchgate.net/publication/366903090
23. Widarti, Nurqaidah. Analisis Kadar Serum Glutamic Pyruvic Transaminase (SGPT) dan Serum Glutamic Oxaloacetic Transaminase (SGOT) Pada Petani Yang Menggunakan Pestisida. Jurnal Media Analis Kesehatan. 2019 Jun;10(1):35–43. https://doi.org/10.32382/mak.v10i1.
24. Al-Bidhani FHJ. Effect of aspirin administration on body weight and liver enzymes in male rats. Annals of Medical Physiology. 2021 Dec 31;5(3):13–6. https://doi.org/10.23921/Amp.2021v5i3.00051.
25. Moriles KE, Zubair M, Azer SA. Alanine Aminotransferase (ALT) Test. StatPearls [Internet]. 2024 Feb 27 [cited 2024 Jun 21]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK559278/.
26. Kendaran AAS, Arjana AAG, Pradnyantari ASI. Aktivitas Enzim Alanine-Aminotransferase dan Aspartate Aminotransferase pada Tikus Putih Jantan yang Diberi Ekstrak Buah Pinang. Buletin Veteriner Udayana [Internet]. 2017 Aug;9:132. Available from: http://ojs.unud.ac.id/index.php/buletinvet.
27. Allameh A, Niayesh-Mehr R, Aliarab A, Sebastiani G, Pantopoulos K. Oxidative Stress in Liver Pathophysiology and Disease. Antioxidants. 2023 Sep 1;12(9). https://Doi.Org/10.3390/Antiox12091653.
28. Fadlilah AR, Lestari K. Review: Peran Antioksidan Dalam Imunitas Tubuh. Farmaka. 2023 May 23;21(2):171-178. https://doi.org/10.24198/farmaka.v21i2.45929.
29. Santacroce G, Gentile A, Soriano S, Novelli A, Lenti MV, Di Sabatino A. Glutathione: Pharmacological aspects and implications for clinical use in non-alcoholic fatty liver disease. Front Med (Lausanne). 2023 Mar 22;10. https://doi.org/10.3389/Fmed.2023.1124275.
30. Rusmini, Taurina W, Andrie M. Standardization of Simplicia Golden Sea Cucumber (Stichopus hermanii) from Pelapis Island, West Kalimantan. Majalah Obat Tradisional. 2022;27(2):146–52. https://doi.org/10.22146/Mot.74667.
31. Datta S, Aggarwal D, Sehrawat N, Yadav M, Sharma V, Sharma A, et al. Hepatoprotective effects of natural drugs: Current trends, scope, relevance and future perspectives. Phytomedicine. 2023 Dec;121:155100. https://Doi.Org/10.1016/J.Phymed.2023.155100.
32. Li S, Zhou Y, Sun L, Wang Y, Song S, Ai C, et al. Effects of Storage Method on the Quality of Processed Sea Cucumbers (Apostichopus japonicus). Foods. 2022 Dec 19;11(24):4098. https://doi.org/10.3390/Foods11244098
33. QI X, YIN M, QIAO Z, LI Z, YU Z, CHEN M, et al. Freezing and frozen storage of aquatic products: mechanism and regulation of protein oxidation. Food Science and Technology. 2022;42. https://doi.org/10.1590/Fst.91822.
34. Ge X, Wang H, Yin M, Wang X. Effect of Different Thawing Methods on the Physicochemical Properties and Microstructure of Frozen Instant Sea Cucumber. Foods. 2022 Aug 29;11(17):2616. https://doi.org/10.1590/Fst.91822.
35. Cai L, Wan J, Li X, Li J. Effects of different thawing methods on physicochemical properties and structure of largemouth bass (Micropterus salmoides). J Food Sci. 2020 Mar 1;85(3):582–91. https://doi.org/10.1111/17503841.15029.
36. Susanto H, Safithri M, Tarman K. Antibacterial activity of Stichopus hermanii and Stichopus variegatus methanol extract (Aktivitas Antibakteri

Ekstrak Metanol Stichopus hermanii dan Stichopus. 2018;5(2):1–11. Available from: http://biokimia.ipb.ac.id.
37. Monika R, Pringgenies D, Setyati WA. Potensi Ekstrak Teripang Stichopus hermanii, Semper 1868 (Holothuroidea : Stichopodidae) sebagai Penghasil Senyawa Antibakteri terhadap Streptococcus mutans Clarke, 1924 (Bacilli : Streptococcaceae). J Mar Res. 2021 Aug 2;10(3):421–7. https://doi.org/10.14710/Jmr.V10i3.31097.
38. Sekarsari S, Widarta IWR, Jambe AAGNA. Pengaruh Suhu Dan Waktu Ekstraksi Dengan Gelombang Ultrasonik Terhadap Aktivitas Antioksidan Ekstrak Daun Jambu Biji (Psidium Guajava L.) . 2019;8(3):267–77. https://doi.org/10.24843/itepa.2019.v08.i03.p05.
39. Wendersteyt NV, Wewengkang DS, Abdullah SS. Uji Aktivitas Antimikroba Dari Ekstrak Dan Fraksi Ascidian Herdmania Momus Dari Perairan Pulau Bangka Likupang Terhadap Pertumbuhan Mikroba Staphylococcus aureus, Salmonella typhimurium dan Candida albicans. Journal of Pharmacon. 2021 Feb;10(1):706–12. https://doi.org/10.35799/pha.10.2021.32758.
40. Riwanti P, Izazih F. Artikel Penelitian Pengaruh Perbedaan Konsentrasi Etanol pada Kadar Flavonoid Total Ekstrak Etanol 50,70 dan 96% Sargassum polycystum dari Madura. J-PhAM Journal of Pharmaceutical Care Anwar Medika. 2020;82(2):2654–8364. http://dx.doi.org/10.36932/jpcam.v2i2.1.
41. Anggraini W, Wulandari Rousdy D, Rusmiyanto Pancaning Wardoyo E, Hadari Nawawi JH, Barat K. Nilai Malondialdehid Hepar Mencit Yang Diinduksi Parasetamol Pada Pemberian Ekstrak Metanol Kulit Kayu Vitex Pubescens Vahl. Jurnal Protobiont. 2021;10(1):6–11. https://jurnal.untan.ac.id/index.php/jprb/article/view/50760/75676591258.
42. Nurfitriani E, Mulyani Y, Untung Kurnia Agung M. Hubungan Kualitas Air dengan Profil Metabolit Sekunder Ekstrak Daging Holohuria atra di Perairan Teluk Lampung dan Perairan Garut. Vol. 2, Jurnal Akuatika Indonesia.2017. https://doi.org/10.24198/jaki.v2i2.
43. Ilyas Yusuf M, Wulaisfan R. Uji Toksisitas Akut dan Gambaran Histopatologi Hepar Mencit yang Diberi Ekstrak Terpurifikasi Daun Galing (Cayratia trifolia L. Domin). Jurnal Farmasi. 2018;4(1):12–5. http://dx.doi.org/10.33772/pharmauho.v4i1.4623.
44. Masrifah NR, Abram PH. Uji Aktivitas Antioksidan Ekstrak Daun dan Kulit Labu Air (Lagenaria siceraria (Molina) Standl.). Jurnal Akademika Kim. 2017 May;2(2):98–06. https://doi.org/10.22487/j24775185.2017.v6.i2.9240.
45. Sotler R, Poljšak B, Dahmane R, Jukić T, Pavan Jukić D, Rotim C, et al. Prooxidant Activities of Antioxidants and Their Impact on Health. Vol. 58, Acta clinica Croatica. NLM (Medline); 2019. p. 726–36. https://doi.org/10.20471/Acc.2019.58.04.20.