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EFFECT OF GOLDEN SEA CUCUMBER EXTRACT (*STICHOPUS HERMANII*) ON HEPATIC TISSUE CATALASE LEVELS IN WHITE RATS (*RATTUS NORVEGICUS*) INDUCED WITH HIGH DOSE ASPIRIN

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ABSTRACT

Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is widely used for its analgesic, antipyretic, and anti-inflammatory effects but may cause adverse effects, including hepatotoxicity. Lipid peroxidation can disrupt red blood cell function, countered by antioxidant enzymes like catalase (CAT), which is highly concentrated in the liver. This study examines the effect of golden sea cucumber (Stichopus hermanii) extract on hepatic CAT levels in aspirin-induced rats. A laboratory experiment used 24 male Wistar rats (2-3 months old, 150-200 g), divided into four groups: K1 (control, standard feed), K2 (aspirin 250 mg/kgBW), K3 (sea cucumber extract 97.2 mg/200gBW + aspirin 250 mg/kgBW), and K4 (sea cucumber extract 194.4 mg/200gBW + aspirin 250 mg/kgBW). Hepatic CAT levels were measured, yielding averages of K1 = 534.86 U/mg, K2 = 525.76 U/mg, K3 = 621.33 U/mg, and K4 = 565.24 U/mg. Normality and homogeneity tests confirmed data distribution assumptions. One-way ANOVA analysis showed no significant difference ($p = 0.362$, $p > 0.05$) between groups, indicating that golden sea cucumber extract did not significantly affect hepatic CAT levels in aspirin-induced rats. In conclusion, while Stichopus hermanii extract slightly increased CAT levels in some groups, the effect was not statistically significant. Further research is needed to explore alternative mechanisms or dosages that may enhance the hepatoprotective role of sea cucumber extract against aspirin-induced toxicity.

KEYWORDS *Catalase, Aspirin, Golden sea cucumber (Stichopus hermanii)*

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INTRODUCTION

Indonesia, as a developing country, is still faced with significant challenges in overcoming various health problems. Infectious diseases are still considered high, but the prevalence of degenerative diseases is increasing. Some degenerative conditions, including cancer, diabetes mellitus and related complications, as well as atherosclerosis which is the cause of heart, vascular disease and stroke are the result of pathophysiology by oxidative stress.(Werdhasari, 2014)

Exposure to high levels of *Reactive Oxygen Species* (ROS) can cause chronic oxidative stress, which can cause significant damage to the human body, such as in ischemia or hepatic reperfusion. (Cichoz -Lach and Michalak, 2014)Oxidative stress is a condition that reflects an imbalance between free radicals that are prooxidants and antioxidants that play a role in maintaining tissue stability to prevent damage (Munandar, 2023).

The liver is an organ whose role is very crucial and important for the body, some of these roles include as the body's defense against microbes and detoxification of drugs and harmful substances. In the case of mild disorders, liver function can still be maintained, but it will worsen and be fatal if more severe disorders occur (Widowati and Rinata, 2020)(Tandi, 2017).

Aspirin belongs to the class of *Nonsteroidal Anti-Inflammatory Drugs* (NSAIDs) commonly used as analgesics, antipyretics, and anti-inflammatory. A number of studies state that aspirin has a positive effect by making a number of changes in the antioxidant system and does not have harmful effects (Mossa, Heikal and Mohafrash, 2014; Ricciotti, Wangensteen and FitzGerald, 2021). The negative impact of NSAIDs is found through the way they bind to a number of metal cations that are important for the body's physiology so that they can cause gastrointestinal irritation, bleeding, impaired kidney function, skin eruptions, impact on hearing, and hepatotoxicity.(Mossa, Heikal and Mohafrash, 2014)

One of the ways pesticides can become toxic is through *Lipid Peroxidation* (LPO), which can interfere with the biochemical and physiological functions of red blood cells. To protect themselves, red blood cells are equipped with effective antioxidant enzymes, such as *Superoxide Dismutase* (SOD), *catalase* (CAT), and *Glutathione Peroxide* (GPx). This system is in charge of neutralizing reactive oxidants into species that are less reactive or not reactive at all.(Mossa, Heikal and Mohafrash, 2014)

CAT is found in a number of organs of the body. This enzyme can be easily found in the kidneys, bone marrow, blood and is most commonly found in the liver. The body is protected from *hydrogen peroxide* (H2O2) by the enzyme catalase, which is a type of hydroperoxidase (Inayah et al ., 2022).

Patients who take moderate to high doses of aspirin in the long term as therapy often experience elevated levels of ALT (*Alkaline Transferase*), ALP (*Alkaline Phosphatase*), and bilirubin. High doses of aspirin can cause symptoms such as nausea, anorexia, as well as discomfort in the abdomen, even up to encephalopathy characterized by signs of liver dysfunction such as increased ammonia and blood clotting disorders (Bathesda, 2017).

Antioxidants (reductors) are considered very important and necessary by the body because antioxidants can overcome and prevent oxidative stress.

Antioxidants act as substances that are able to maintain stability and/or activate free radicals before human body cells are attacked. (Werdhasari, 2014; Munandar, 2023)(Zalukhu, Phyma and Pinzon, 2016)

Antioxidants are believed to boost the antioxidant system in the body which makes it one of the options for dealing with a number of diseases, especially those involving oxidative stress(Casas-Grajales, 2015). Golden sea cucumber (*Stichopus hermanii*) is considered to have high *Eicosapentaenoic* (EPA) and *Docosahexaenoic Acid* (DHA) activities. It is determined by the activity of SOD which functions to prevent oxidative stress(Yatmasari, Setianingsih and Riami, 2021). Data related to the use of marine life as a medicinal raw material is still very minimal in Indonesia so that the use of golden sea cucumber can be an innovation for the prevention and treatment of diseases as previously explained(Central Agency Statistics, 2016; Mulawarmanti, 2019)**.**

Based on this background, the researcher wanted to find out how the effect of administering golden sea cucumber extract (*Stichopus hermanii*) on the catalase level of aspirin-induced liver tissue at high doses through experimental analytical methods. This research is expected to increase the production of the use of marine biota as a therapy and source of antioxidants that can be consumed by the wider community.

This study aims to determine the effect of administration of golden sea cucumber extract *Stichopus hermanii* on the level of liver tissue catalase induced by high doses of aspirin. In particular, this study seeks to prove that aspirin doses of 250 mg/KgBB can affect the level of catalase liver in rats as well as the effectiveness of two doses of golden sea cucumber extract, namely 97.2 mg/200gBB and 194.4 mg/200gBB, as a medium for the prevention of liver disease. Theoretically, the results of the study are expected to provide new insights into the effect of golden sea cucumber extract on the liver, enrich the experience of researchers, and become an academic reference for Hang Tuah University. Practically, this research is expected to provide additional insight for medical personnel about the benefits of golden sea cucumber in the prevention of liver disease and provide knowledge to the wider community so that they can use golden sea cucumber as a medicinal ingredient to maintain liver health.

RESEARCH METHOD

This study uses a post-test only control group design method with four treatment groups. Experimental animals in the form of male white rats of the Wistar strain were randomly divided into a negative control group, a positive control, and two treatment groups. The negative control group was only given standard feed and drinking water. The positive control group was induced with high-dose aspirin (250 mg/kgBB) from day 13 to day 24. Treatment group 1 received a dose of 97.2 mg/200gBB of golden sea cucumber extract orally for 12 days, followed by administration of high doses of aspirin from day 13 to day 24. Treatment group 2 received a dose of 194.4 mg/200gBB of golden sea cucumber extract with a similar treatment pattern. On the 24th day, the catalase level of liver tissue was measured

using a spectrophotometer with a wavelength of 350 nm to assess the impact of the treatment on these parameters.

Prior to treatment, the mice were subjected to a 7-day adaptation period in a laboratory under controlled conditions (adequate ventilation, humidity, and nutrition). The trial animals were divided into 4 treatment groups at random. Golden sea cucumber extract is prepared by ethanol extraction process, while aspirin solution is made by mixing aspirin in a 1% CMC-Na solution. The treatment was given according to the group design for 23 days. At the end of the treatment, the liver tissue is removed through a post-anesthesia surgical process. Tissue samples were homogenized with phosphate buffers, then H2O2 solution was added to measure catalytic activity using a spectrophotometer. The data obtained were analyzed using SPSS through normality test (Saphiro-Wilk), homogeneity test (Levene's test), and ANOVA or Kruskal-Wallis test according to the data distribution. The results of the analysis were used to determine the significant effect of administering golden sea cucumber extract on the catalase level of rat liver tissue.

RESULT AND DISCUSSION

Research Data

The research data was obtained after conducting research for 24 days at the Hyperbaric Laboratory, Faculty of Medicine, Hang Tuah University, Surabaya. The research data was taken from white rats of the Wistar strain (*Rattus norvegicus*) which were divided into 4 groups of experimental animals as follows:

Negative control group (K1)	:	Supplied with standard drinking and feed
Positive control group (K2)	:	Aspirin-induced dose 250 mg/kgBB
Treatment group 1 (K3)	:	Given a dose of 97.2 mg/200gBB of golden sea cucumber extract, then given a dose of 97.2 mg/200gBB of golden sea cucumber extract and aspirin at a dose of 250mg/kgBB
Treatment group 2 (K4)	:	Given golden sea cucumber extract at a dose of 194.4 mg/200gBB, then given golden sea cucumber extract at a dose of 194.4 mg/200gBB and aspirin at a dose of 250mg/kgBB

The research data was analyzed using *Statistical Product and Service* (SPSS). The level of significance for analyzing statistics ($\alpha = 0.05$) i.e. p value < 0.05 is considered significant. The normality test used *Saphiro-Wilk* because the number of research samples was less than 50. If the results have a significance of $p > \alpha$, then the data are normally distributed and a homogeneity test can be performed with *Levene's test*. If the results *of Levene's test* have a significance of $p > \alpha$, then the data are considered homogeneous and can be continued with different tests. Data that is normally distributed and homogeneous can use *One-way ANOVA* because the study is more than 2 groups, while data that are not normally distributed or heterogeneous can analyze data using the *Kruskal-Wallis test.* The results of the differential test showed $p < \alpha$, the results were declared significant.

The results of measuring the catalase level of liver tissue in each sample of the negative control group (K1), positive control group (K2), treatment group 1 (K3), and treatment group 2 (K4) are available in Table 1.

Table 1 Liver Tissue Catalase Levels Per Trial Animal

No.	K1 (U/mg)	K2 (U/mg)	K3 (U/mg)	K4 (U/mg)
1.	491,67	510	602	415,67
2.	608	344	613,33	436,67
3.	619,33	636	744,33	538,67
4.	681,67	472	714,33	588,33
5.	483,67	466,33	745,33	579
6.	393,67	745,33	468,67	663,67
7.	466	506,67	461,33	569

The average value and standard deviation of the catalase level of liver tissue in each group of experimental animals can be seen in Table 2.

Table 2 Average Value and Standard Deviation of Liver Tissue Catalase Levels Per Group of Experimental Animals

	K1 (U/mg)	K2 (U/mg)	K3 (U/mg)	K4 (U/mg)
Average	534,86	525,76	621,33	565,24
Std. deviation	102,63	129,38	121,45	68,21

Based on these data, it is known that there is a decrease in the average level of hepatic tissue catalase in the positive control group (K1) when compared to the negative control group (K2). The average increase in hepatic tissue catalase levels occurred in treatment group 1 (K3) and decreased again in treatment group 2 (K4). Figure 5.1 provides information related to the average level of hepatic tissue catalase in each group in the form of a diagram.

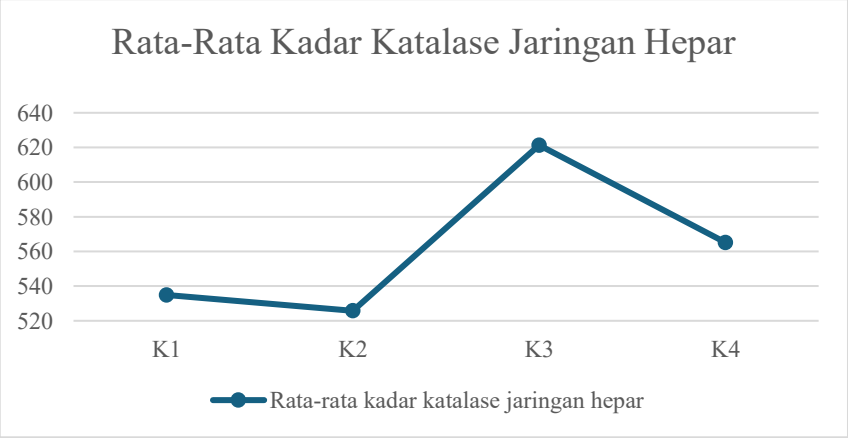

Figure 1 Average Liver Tissue Catalase Levels

Results of Normality Test of Liver Tissue Catalase Levels

The total sample used in the study was less than 50 which was the reason for the normality test using *Saphiro-Wilk*. The results of the normality test of each

group can be seen in table 3.

Table 3 Saphiro-Wilk Normality Test

Parameter	Group	Mr.
Liver tissue catalase levels	K1	0,620
	K2	0,616
	K3	0,161
	K4	0,312

Description of the Saphiro-Wilk *normality test*:
H0 : Normal distributed data, p > 0.05
H1 : Normal undistributed data, p < 0.05

Based on the results of the normality test in Table 3, it can be seen that the significance value in K1 is 0.620, K2 is 0.616, K3 is 0.161, and K4 is 0.312. From these results, it can be concluded that all of them have a significance value of p > 0.05 so that the data are distributed normally and H0 is accepted.

Results of Homogeneity Test of Liver Tissue Catalase Levels

Once the normality requirements have been met, the next step is to ensure that the data groups we compare have the same level of diversity as the homogeneity test. *Levene's test* can be used to compare more than two groups according to the study. The test results with a p > value of 0.05 indicate the homogeneity of the variant. On the other hand, a p-< value of 0.05 indicates non-homogeneous data. The results of the homogeneity test of each group can be seen in Table 4.

Table 4 The Levene's Homogenitas Test

Parameter	Levene Statistic	df1	df2	Mr.
Liver tissue catalase levels	0,554	3	24	0,333

Description of the homogeneity test results using *Levene's Test*:
H0 : Data homogen, p > 0.05
H1 : Inhomogeneous data, p < 0.05

Based on Table 4 in the significance column, it shows a figure of 0.333 so that H0 is accepted because the significance value p > 0.05. It can be concluded that the results of the homogeneity test are homogeneous data and H0 is accepted.

Results of Differential Test of Liver Tissue Catalase Levels

The One-way ANOVA *test* was carried out because the samples were more than 2 groups, normally distributed, and homogeneous variance. The *One-way ANOVA test* was carried out to find out whether there was a difference in the research results or not. The results of the different tests for each group can be seen in Table 5.

Table 5 ANOVA One-way Difference Test

Parameter	Group	Average	Std. Deviation	p value
Liver tissue catalase levels	K1	534,86	102,63	0,362
	K2	525,76	129,38	
	K3	621,331	121,45	

K4	565,24	68,21

Description of different test results using *the One-way ANOVA test*
H0 : Data is not significant, $p > 0.05$
H1 : Significant data, $p < 0.05$

Based on the results of *the One-way ANOVA test* in table 5, a significance result of 0.362 ($p>0.05$) was obtained, which means that H0 was accepted and H1 was rejected. This shows that the data is not significant and there is no significant difference between K1, K2, K3, and K4.

This study was conducted with the aim of determining the effect of administering golden sea cucumber extract (*Stichopus hermanii*) on the catalase level of white rat liver tissue (*Rattus norvegicus*) which is induced by high doses of aspirin. The average results of hepatic tissue catalase levels in the group of experimental animals that were not treated were 534.86 U/mg, the high-dose aspirin-induced experimental animal group was 525.76 U/mg, the experimental animal group induced golden sea cucumber extract (*Stichopus hermanii*) dose of 97.2 mg/200gBB and high dose aspirin concurrently with golden sea cucumber (*Stichopus hermanii*) dose of 97.2 mg/200gBB was 621.33 U/mg, and the group of experimental animals induced golden sea cucumber extract (*Stichopus hermanii*) dose of 194.4 mg/200gBB and high dose aspirin concurrently with golden sea cucumber (*Stichopus hermanii*) dose of 194.4 mg/200gBB is 565.24 U/mg. These results show that the administration of the extract *Stichopus hermanii* The four groups did not provide a significant difference ($p = 0.362$).

This study showed different but meaningful levels or activity of hepatic catalase in each group. The highest catalase levels were possessed by the group of experimental animals induced by golden sea cucumber extract (*Stichopus hermanii*) dose of 97.2 mg/200gBB and high dose aspirin concurrently with golden sea cucumber (*Stichopus hermanii*) dose of 97.2 mg/200gBB as treatment group 1. The positive control group, namely the experimental animal group induced by high doses of aspirin, had the lowest levels of catalase.

Effect of Aspirin 250mg/kgBB on Rats' Liver Catalase Levels

Aspirin is an analgesic and antipyretic drug from the NSAID class that is the most commonly used almost worldwide. Higher doses of aspirin and continuous administration have been shown to be effective in the treatment of juvenile rheumatoid arthritis, systemic lupus erythematosus, rheumatoid arthritis, acute rheumatic fever, and Kawasaki disease. The use of aspirin in children or adolescents should be avoided because it risks causing *Reye syndrome* (Bethesda, 2017).

The dose of aspirin given varies based on the age of the patient and the disease he or she is experiencing. A single dose of aspirin of 300 mg/day may double the risk of bleeding compared to a dose of 100 mg/day. This can support the claim that higher doses correlate with greater levels of harm. Aspirin at a dose of 250 mg/kgBB 1×1 is considered to have passed the therapeutic dose because the recommended dose for aspirin used as an antipyretic and analgesic in children is between 50-75 mg/kgBB/day. (Lintong, Loho and Budget, 2013; Fathurida, 2020)

This can be reviewed in K2 as a positive control that has lower levels or catalase activity when compared to K1 as a negative control. Long-term use of

doses of 250 mg/KgBB can cause moderate to severe toxicity. This is very much in line with research that aspirin doses of 70 mg/kg, 100 mg/kg, 105 mg/kg, 140 mg/kg, 200 mg/kg, and 600 mg/kg can cause histopathological changes in the liver Fathurida (2020)(Fathurida, 2020)

Effect of Golden Sea Cucumber Extract (*Stichopus hermanii*) 97.2 mg/200gBB as Hepatoprotective Media

Liver damage can be detected through decreased activity of enzymatic antioxidants known as catalase. Catalase, an enzyme in the liver, provides the body's protection from harmful substances by converting hydrogen peroxide into water and oxygen. These antioxidants are very important in overcoming oxidative stress by supplying one electron to oxidize the molecule. It is played by the flavonoids contained in (Hapsari *et al.*, 2023)*Stichopus hermanii*, which make it an antioxidant and anti-inflammatory as well as a protector of cell structure. (Husna, Kairupan and Lintong, 2022; Dewi and Ma'ruf, 2023)

The results that can be seen from K3 as treatment group 1 are in line with the theory and research. The increase in catalase levels of K2 compared to K3 has a significant insignificant difference. This proves that the antioxidant content in *Stichopus hermanii* at a dose of 97.2 mg/200gBB can protect liver cells to avoid oxidative stress caused by high doses of aspirin.

Effect of Golden Sea Cucumber Extract (*Stichopus hermanii*) 194.4 mg/200gBB as Hepatoprotective Media

Increased doses of antioxidants can cause many organs to be exposed, resulting in a heavier workload. In the case of potentially fatal toxic effects, various organs will fail in succession. Adverse effects occur when these substances are consumed in significantly higher amounts. Toxicity will arise when harmful compounds accumulate in the liver and kidneys in high concentrations because they greatly affect the degree of absorption, distribution, binding, and excretion.(Dewi and Ma'ruf, 2023)

Treatment group 2 or K4 is suspected to experience the same thing as the theory previously explained. This can be seen from the level of catalase which when compared to K3 experienced an insignificant but meaningful decrease. An increase in the dose of *Stichopus hermanii* 2×fold in K4 is considered to have side effects derived from the content of *Stichopus hermanii*.

Research conducted that explains that flavonoids are also found to have negative effects. Concurrent administration of large doses to rats can cause disturbances in vital signs, including body temperature, pulse, respiratory function, blood pressure, and can even lead to death.Dewi and Ma'ruf (2023)(Dewi and Ma'ruf, 2023)

The alkaloid content in *Stichopus hermanii* is also suspected to have considerable side effects. Many alkaloids are toxic to mammals, although most are also used as medicines. Alkaloids from the *pyrrolizidine* group are known to have toxic properties, especially against the liver (hepatotoxic), as well as can stimulate the formation of cancer (carcinogenic), cause cell mutations (mutagenic), and cause abnormalities in the fetus (teratogenic). In severe cases, exposure to these alkaloids

can result in serious liver damage and even lead to death(Dewi and Ma'ruf, 2023).

Sample *Drop Out* in Research

In this study, three dead samples were found during the study, namely one rat in K1, one rat in K2, and one rat in K3. From the three samples, no injuries were found on the outermost part of the body from the sample. The three drop-out samples occurred in mice that had the thinnest weight and their fur looked unhealthy. Possible reasons for the deaths of the samples include stress, sick rats, and side effects from the treatment given.

CONCLUSION

Based on laboratory experimental research on the effect of administration of golden sea cucumber extract *Stichopus hermanii* on the catalase levels of white rat liver tissue *Rattus norvegicus* induced by high doses of aspirin, it was concluded that aspirin with a dose of 250 mg/KgBB could significantly reduce liver catalase levels. The administration of golden sea cucumber extract at a dose of 97.2 mg/200gBB was effective in increasing catalase levels, making it a potential medium for the prevention of liver disease, while the dose of 194.4 mg/200gBB did not show similar effectiveness. Further research is suggested to conduct phytochemical and toxicity tests of golden sea cucumber extract, as well as exploration of dosage variations in both sea cucumber extract and aspirin to determine the minimum and maximum doses that are effective in supporting the catalase function of liver tissue.

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