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Short Communication

Sea Cucumber Extract (*Phyllophorus sp.*) Reduces Hepatic Malondialdehyde Levels in High-Fat Diet-Induced Liver Injury in Wistar Rats

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ABSTRACT

Malondialdehyde (MDA) is a key biomarker of lipid peroxidation and hepatic oxidative damage. Natural compounds such as sea cucumber (*Phyllophorus sp.*), have gained attention as potential therapeutic candidates. This research aimed to assess the impact of *Phyllophorus sp.* extract on hepatic MDA levels in high-fat diet (HFD)-induced liver injury in rats. Thirty male Wistar rats were divided into five groups of 6 rats each: Normal control (KN) (Standard diet), Negative control (K-) (HFD for 28 days), Positive control (K+) [HFD + Simvastatin (1.2 mg/kg) for 7 days], Treatment 1 (KP1) [HFD + *Phyllophorus sp.* extract (8.5 mg/kg) for 7 days], and Treatment 2 (KP2) [HFD + *Phyllophorus sp.* extract (17 mg/kg) for 7 days]. After 28 days, hepatic MDA levels were measured, and statistical analyses were performed. Results showed that HFD significantly ($p < 0.001$) increased hepatic MDA levels with MDA levels of 3134.67, 3336.00, 3046.83, and 3633.17 nmol/g in the KP1, KP2, and K+ groups, respectively compared to the normal control with MDA level of 1429.67 nmol/g. MDA level in *Phyllophorus sp.* extract treated group at 17 mg/kg (KP2) was significantly lower than that of the positive control (simvastatin). However, no significant differences were founded between positive control and treatment 1 ($p = 0.322$) or treatment 1 and treatment 2 ($p = 0.335$). These findings suggest that *Phyllophorus sp.* extract effectively reduces hepatic oxidative stress in HFD-induced rats, with hepatoprotective effect similar to simvastatin, therefore highlighting its potential as a natural therapeutic candidate for HFD-induced liver injury.

Keywords: *Phyllophorus sp.*, Sea Cucumber Extract, Malondialdehyde, High-Fat Diet, Oxidative Stress, Wistar Rats.

Introduction

Given its relationship with metabolic disorders and the potential to progress to more serious liver disease, non-alcoholic fatty liver disease (NAFLD) poses considerable challenges globally. In Indonesia, the increased prevalence of hyperlipidemia (particularly hypertriglyceridemia) alongside high dietary fat consumption represents the leading risk factors for NAFLD.[1,2] A key mechanism driving the progression and poor outcomes of NAFLD is oxidative stress. NAFLD is the accumulation of fat in the liver occurring without substantial alcohol consumption. Malondialdehyde (MDA) is often used as a key marker of lipid peroxidation. As a prominent biomarker, MDA indicates lipid peroxidation and oxidative damage, particularly in hepatic tissues, thereby providing a clue to the extent of cellular damage.[3–5] Currently, statins, such as simvastatin, are frequently prescribed to manage dyslipidemia and mitigate cardiovascular risk. However, these medications have some limitations, particularly with respect to their long-term efficacy and ability to manage oxidative stress.[6] As a result, increasing attention has been directed toward natural products with antioxidant and hepatoprotective activities as potential complementary therapies.

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There is a growing exploration of natural marine-derived substances for their use as alternative pharmaceuticals. Sea cucumbers, particularly the species *Phyllophorus sp*, stand out among these promising natural sources. They are rich in bioactive compounds, including saponins, triterpenes, and peptides that have demonstrated a variety of beneficial effects, such as antioxidant, anti-inflammatory, and lipid-lowering capabilities.[7,8] Previous animal studies have vividly illustrated the lipid-lowering and anti-inflammatory effects of sea cucumber extract, particularly in models of diet-induced obesity, showcasing its potential as a therapeutic agent.[9,10] While the correlation between oxidative stress and NAFLD has been well established, there remains limited evidence regarding the role of marine-derived bioactive compounds, particularly sea cucumber (*Phyllophorus* sp.), in mitigating hepatic oxidative damage. Numerous studies have demonstrated the antioxidant and lipid-lowering effects of various natural products; however, only a few have specifically investigated the direct impact of *Phyllophorus* sp. extract on hepatic MDA levels as a marker of lipid peroxidation in high-fat diet–induced NAFLD models. Therefore, this study was designed to address this gap by evaluating the potential of *Phyllophorus* sp. extract to reduce hepatic oxidative stress and provide hepatoprotective benefits better than simvastatin. This study aims to analyze the effect of *Phyllophorus sp*. extract on hepatic MDA levels in Wistar rats fed with High-Fat Diet (HFD). It was hypothesized that the extract would decrease liver oxidative stress, thereby providing a promising natural approach to managing liver health and mitigate the negative consequences of high-fat consumption.

Materials and Methods

Collection and identification of sea cucumber

Sea cucumbers were collected in July 2023 from the coastal area of Surabaya, East Java, Indonesia. The specimens were taxonomically

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identified at the Laboratory of Biosciences and Plant Technology, Department of Biology, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia. Taxonomic identification confirmed the species as *Phyllophorus sp*. (Phylum Echinodermata, Class Holothuroidea, Order Dendrochirotida, Family Phyllophoridae). A voucher specimen was deposited in the Biosciences and Plant Technology Laboratory, ITS, under the voucher number 010/IT.1/Biosains dan Teknologi Tumbuhan/2023 for future reference.

Preparation of Phyllophorus sp. extract

Fresh sea cucumbers (*Phyllophorus* sp.) were dissected to remove their internal organs, washed with water, and drained. A total of 3 kg of fresh sea cucumbers were cut into several small pieces and dried in a freeze dryer at –46°C and a pressure of 5 mTorr until completely dehydrated. The dried sea cucumbers were ground into a fine homogenous powder. The powdered sea cucumber (300 g) was macerated in 96% ethanol (3 L) at room temperature for 3 × 24 h with occasional stirring to ensure complete extraction of bioactive compounds. The extract was filtered, and the obtained filtrate was subsequently concentrated using a rotary evaporator at 40°C to obtain a thick ethanol extract of *Phyllophorus* sp.[11]

Animals

Male rats (*Rattus norvegicus*) of the Wistar strain were obtained from the Hyperbaric and Integrated Biomolecular Laboratory, Faculty of Medicine, Hang Tuah University. The rats were housed in well-ventilated cages and acclimatized to the laboratory environment for 7 days with adequate feed and water.[5]

Ethical consideration

Ethical clearance (Certificate No. I/050/UHT.KEPK.03/VIII/2025) was issued by the Health Research Ethics Committee of Faculty of Medicine, Hang Tuah University. The study was executed in full compliance with international guidelines and regulations for the use of animals in experiments.

Experimental design

The experiment used a post-test only control group design. Thirty adult male Wistar rats (10 weeks, body weight (BW) of 100 and 200 g), were randomly divided into five groups, each consisting of six animals: Normal control group (KN) which received a standard diet, which served as a baseline for evaluating the impact of other dietary interventions; Negative control group (K−) which were asministered a high-fat diet (HFD) for a continuous period of 28 days; Positive control group (K+) which after 21 days on the HFD, were continued with the standard diet, then given simvastatin at 1.2 mg/kg BW for the subsequent 7 days to provide a reference point for evaluating the effectiveness of the treatments; treatment 1 group (KP1) which were fed the HFD for 21 days, after which they were given the HFD along with *Phyllophorus sp*. extract at 8.5 mg/kg BW for 7 days to explore the potential therapeutic effect of *Phyllophorus sp.* extract; and treatment 2 group (KP2) which received the HFD for 21 days, followed by the administration of a higher dose of *Phyllophorus sp.* extract (17 mg/kg BW) for the following 7 days, allowing for a direct comparison of dose-dependent effects.[11]

Both the extract and simvastatin were administered orally via a specialized gastric sonde, ensuring accuracy in dosing and minimizing stress to the animals. The treatment phase was concluded by euthanizing the rats humanely. Immediately following euthanasia, liver tissues were carefully harvested, then homogenized to generate the samples required for biochemical analysis.[5]

Hepatic malondialdehyde (MDA) levels measurement

Hepatic MDA levels were measured using a modified Thiobarbituric Acid Reactive Substances (TBARS) assay combined with spectrophotometric analysis for accurate quantification. Approximately 100 mg of liver tissue was homogenized in 1 mL of 0.1 M phosphate buffer (pH 7.0) containing phenylmethanesulfonyl fluoride (PMSF) using a micropestle and homogenizer, then centrifuged at 5000 rpm for 10 minutes. The resulting supernatant was collected for MDA measurement.[12]

Modified methos of thiobarbituric acid reactive substances was conducted by mixing 200 µL of the supernatant with 200 µL of thiobarbituric acid (TBA) 0.67%, 200 µL of trichloroacetic acid (TCA) 20%, and 200 µL of acetic acid 1% (pH 3.5). The mixture was incubated in a water bath at 95 °C for 60 minutes, then allowed to cool to room temperature and centrifuged at 3000 rpm for 10 minutes. The absorbance of the resulting supernatant was subsequently measured at 532 nm using a UV-Vis spectrophotometer.[12] MDA concentrations were determined using a standard curve generated from 1,1,3,3-tetramethoxypropane (TMP) within a concentration range of 0–10 µM. The results were expressed as nanomoles of MDA per gram of liver tissue. All samples were analyzed in triplicate to ensure measurement reliability and reproducibility.[12]

Statistical analysis

Statistical analyses were carried out using SPSS (IBM Corporation, New York, USA). Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene's test. Differences among group means were determined through one-way ANOVA, followed by the LSD post hoc test. A p-value less than 0.05 was considered statistically significant.

Results and Discussion

Hepatic malondialdehyde (MDA) levels was measured in rats following various treatment interventions. The negative control group (K−) exhibited a high MDA levels, with an alarming concentration of 3134.67 ± 540.51 nmol/g. This elevated level suggests significant oxidative stress in these rats, indicating potential hepatic damage. In stark contrast, the normal control group (KN) showed substantially lower MDA levels, recorded at 1429.67 ± 635.27 nmol/g (Table 1).

Table 1: Hepatic malondialdehyde (MDA) levels in all treatment groups

Treatment group	Malondialdehyde levels (nmol/g)	P-value
Normal control (KN): Standard diet	1429.67 ± 635.27	<0.001
Negative control (K-): HFD for 28 days	3134.67 ± 540.51	
Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	3633.17 ± 431.25	
Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	3336.00 ± 513.02	
Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	3046.83 ± 391.45	

Values are mean ± standard deviation (SD), n = 6.

The MDA levels were significantly different among all groups ($p < 0.001$). Although the MDA levels in the normal control group appeared relatively high for a physiologically healthy liver, the comparisons between the untreated group and the treatment groups were the primary focus of this study. Thus, the present investigation emphasized the effects of *Phyllophorus* sp. extract on MDA levels and the differences observed across all groups, rather than determining whether the MDA levels in the normal control group were within a normal range.

The group administered 17 mg/kg body weight of *Phyllophorus sp.* extract (KP2) showed a significant decrease in MDA levels, measuring 3046.83 ± 391.45 nmol/g. Although this level was lower than that of the K− group, it was quite close to the levels observed in the positive control group (K+), which had a notably high value of 3633.17 ± 431.25 nmol/g, reflective of the potent oxidative effects of the treatment used in that group. This represents a limitation of the present study, as the baseline MDA levels was not measured prior to treatment. Consequently, the extent of MDA reduction following simvastatin administration could not be determined. In this study, the only comparison made was the final MDA levels in all groups, without

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knowing the actual magnitude of MDA reduction. Another possible explanation for the persistently elevated MDA levels in the simvastatin-treated group could be a result of the influence of other factors that may contribute to increased MDA levels, such as vitamin D and calcium deficiencies, which were not assessed in the present study.[12] According to one-way ANOVA, there were significant differences in MDA levels between the groups ($p < 0.001$).

Table 2: Post hoc Least Significant Difference (LSD) test results for hepatic malondialdehyde (MDA) levels between treatment groups

Treatment group		P-value
Normal control (KN): Standard diet	Negative control (K-): HFD for 28 days	<0.001
	Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	<0.001
	Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	<0.001
	Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	<0.001
Negative control (K-): HFD for 28 days	Normal control (KN): Standard diet	<0.001
	Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	0.103
	Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	0.500
	Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	0.768
Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	Normal control (KN): Standard diet	<0.001
	Negative control (K-): HFD for 28 days	0.103
	Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	0.322
	Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	0.057
Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	Normal control (KN): Standard diet	<0.001
	Negative control (K-): HFD for 28 days	0.500
	Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	0.322
	Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	0.335
Treatment 2 (KP2): HFD + *Phyllophorus sp.* extract at 17 mg/kg bw for 7 days	Normal control (KN): Standard diet	<0.001
	Negative control (K-): HFD for 28 days	0.768
	Positive control (K+): HFD + Simvastatin (1.2 mg/kg bw) for 7 days	0.057
	Treatment 1 (KP1): HFD + *Phyllophorus sp.* extract at 8.5 mg/kg bw for 7 days	0.335

The LSD post hoc test provided further clarify, showing that the KN group (normal control) differed significantly from every other treatment group ($p < 0.05$), as presented in Table 2. This finding underscores the importance of the normal control in the study design. No significant differences were observed between positive control and treatment 1 ($p = 0.322$), and between treatment 1 and treatment 2 ($p = 0.335$), but the positive control and treatment 2 showed a trend toward significance ($p = 0.057$). This result implies that *Phyllophorus sp.* Extract has a stronger MDA-lowering effect than simvastatin. This suggests a promising potential for *Phyllophorus sp.* extract as an alternative therapeutic agent in managing oxidative stress-related hepatic damage.

The negative control (K−) group exhibited an MDA level of 3134.67 ± 540.51 nmol/g, which was indeed lower than the positive control (K+) group (3633.17 ± 431.25 nmol/g) but higher than the normal control (KN) (1429.67 ± 635.27 nmol/g). This finding indicates that a high-fat diet induced oxidative stress, as reflected by the increased MDA levels in the K− group compared with the KN group. The relatively higher MDA value observed in the simvastatin-treated group (K+) compared with the negative control may be attributed to the short duration of treatment (7 days), which may not have been sufficient for simvastatin to exert a measurable antioxidant effect. Previous studies have shown that the antioxidant benefits of statins typically appear after longer administration periods. Therefore, the results of this study suggest that while simvastatin effectively lowers lipid levels, its short-term use may not significantly decrease hepatic oxidative stress.

In contrast, the administration of *Phyllophorus sp.* extract in both treatment groups resulted in lower MDA levels (3336.00 ± 513.02 nmol/g for KP1 and 3046.83 ± 391.45 nmol/g for KP2) compared with the K+ group, indicating a potential antioxidant and hepatoprotective effect of the extract. These findings highlight that *Phyllophorus sp.* extract, even within a short treatment period, exhibited better efficacy in reducing hepatic oxidative damage than simvastatin under similar experimental conditions.

This study underscores the significant impact of a high-fat diet on hepatic health, specifically demonstrating that such a diet markedly elevates the levels of malondialdehyde (MDA) in Wistar rats. MDA serves as a critical indicator of oxidative stress, specifically highlighting the harmful effects of lipid peroxidation on liver tissue. The elevation of MDA levels is a compelling marker of cellular oxidative damage, particularly within hepatocytes - specialized liver cells that play a crucial role in metabolism and detoxification when subjected to metabolic stress.[3]

The present findings indicate that the administration of *Phyllophorus sp*. extract leads to a noteworthy and dose-dependent decrease in MDA levels. This suggests that *Phyllophorus sp.* possesses potent antioxidant capabilities, which are crucial for protecting liver cells from oxidative damage. At 17 mg/kg body weight (KP2), the effects observed were better than those achieved with simvastatin, a well-known and widely prescribed medication for lowering cholesterol. The findings indicate that *Phyllophorus sp.* holds promise as a natural alternative or supplemental treatment for managing high blood lipids, potentially replacing or supporting traditional therapies. This assertion is consistent with earlier research that showcased the positive biological effects of bioactive compounds from sea cucumber. These compounds do not only lower lipid levels, decrease inflammation but also boost the body's natural antioxidant defenses.[7,10]

Among the bioactive compounds of *Phyllophorus sp.*, saponins emerge as a key class of compounds recognized for their remarkable ability to inhibit pancreatic lipase activity, an enzyme critical in fat digestion, thereby impacting overall lipid metabolism. They are additionally responsible for regulating the expression of crucial genes in the lipid metabolism pathway, such as liver X receptor beta (LXR-β), sterol regulatory element-binding protein 1c (SREBP-1c), and fatty acid synthase (FAS).[8,13] Furthermore, these saponins boost the function of key endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These enzymes are crucial because they neutralize free radicals and safeguard hepatocytes against oxidative harm, thereby helping to maintain normal cellular integrity and function.[10,14]

In this study, the short duration of 7 days with simvastatin and *Phyllophorus* sp. extract was selected to highlight the early antioxidant response to treatment, which may provide preliminary insights into the potential hepatoprotective role of *Phyllophorus* sp. extract.

Future studies with extended treatment periods will be necessary to validate the long-term therapeutic efficacy of *Phyllophorus* sp. extract. Interestingly, the present observations revealed that rats treated with simvastatin (K+) still exhibited elevated MDA levels after a brief 7-day treatment period. This finding suggests that standard lipid-lowering medications may not confer immediate antioxidant benefits, which is an

important consideration in clinical settings where rapid improvements in oxidative stress markers are desired. The findings in this study are consistent with reports from previous studies which demonstrated that the antioxidant protective effects of simvastatin become significant only after a prolonged treatment period. Moreover, these studies emphasize that for optimal outcomes in reducing oxidative damage, simvastatin is often most effective when used in combination with other antioxidant agents, highlighting the complexity of managing oxidative stress in the liver.[6,8,15]

The efficacy of *Phyllophorus sp.* extract highlights the considerable therapeutic potential of this natural compound, especially in light of its multifaceted biological activities.

Phyllophorus sp. is beneficial not only for lowering lipids but also for its antioxidant, anti-inflammatory, and immunomodulatory effects. These varied mechanisms collectively offer a comprehensive advantage, notably in protecting the liver against major global health concerns like metabolic syndrome and NAFLD.[8,16] Thus, integrating *Phyllophorus sp.* extract into therapeutic strategies may provide a holistic approach to managing liver health and mitigating the adverse effects associated with high-fat diets and metabolic disorders.

This study did not assess lipoprotein profiles, as the primary focus was to evaluate hepatic oxidative stress through MDA levels. Future study that include both lipoprotein and oxidative stress parameters to provide a more comprehensive understanding of the hepatoprotective effects of *Phyllophorus sp.* extract is needed.

Conclusion

The administration of *Phyllophorus* sp. extract for 7 days effectively reduced MDA concentrations, particularly at a dose of 17 mg/kg BW, resulting in hepatic MDA levels lower than that of simvastatin. The present study demonstrated that *Phyllophorus* sp. extract reduced hepatic MDA levels in high-fat diet–induced Wistar rats, suggesting its antioxidant and potential hepatoprotective effects. These findings provide preliminary evidence that marine-derived bioactive compounds may help attenuate oxidative stress in the liver. However, the results should be interpreted with caution, as the study was limited to an animal model, a short treatment duration, and the use of a single biomarker of oxidative stress. Future studies with extended treatment periods, comprehensive lipid and inflammatory markers, and translational approaches are warranted to validate and expand upon these findings.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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