JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i5.50957
JKD (DMJ), Volume 14, Number 5, September 2025 : 247-253

HEPATIC NF-KB AND CYR61 SUPPRESSION BY *HOLOTHURIA SCABRA* METHANOL EXTRACT IN A HIGH-FAT DIET AND DMBA-INDUCED BREAST CANCER MOUSE MODEL

Demes Chornelia Martantingtyas[1*], Raden Ghita Sariwidyantry[1], Hana Ratnawati[2], Teresa Liliana Wargasetya[3], Ardo Sanjaya[4]
[1]Department of Biochemistry, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia
[2]Department of Histology, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia
[3]Department of Pathology, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia
[4]Department of Anatomy, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia

Keywords:
Breast Cancer,
CYR61,
DMBA,
Holothuria scabra, Inflammation,
Liver,
NF-κB

Received: 18 October 2024
Revised: 3 June 2025
Accepted: 3 June 2025
Available online: 1 September 2025

Corresponding Author:
E-mail: demes.cm@med.maranatha.edu

ABSTRACT

Background: The liver plays a critical role in systemic inflammation and metastasis during breast cancer progression, mediated significantly by NF-κB and CYR61. This study evaluates the effects of Holothuria scabra methanol extract (SCME) on hepatic expression of NF-κB and CYR61 in mice with breast cancer induced by a high-fat diet (HFD) and 7,12-dimethylbenz[a]anthracene (DMBA). **Methods:** Female C57BL/6J mice were divided into five groups: normal diet, positive control (HFD + DMBA), and three SCME-treated groups at doses of 0.33, 0.66, and 0.99 g/kg body weight. NF-κB and CYR61 expression levels in liver tissue were assessed by semi-quantitative RT-PCR. **Results:** SCME treatment significantly reduced hepatic NF-κB and CYR61 gene expression in a dose-dependent manner. The highest SCME dose (0.99 g/kg) markedly downregulated both genes compared to the positive control group ($p < 0.05$). **Conclusion:** Holothuria scabra methanol extract demonstrates promising anti-inflammatory and anticancer activities by modulating NF-κB and CYR61 hepatic expression. Further mechanistic studies and clinical validations are recommended.

INTRODUCTION

The liver plays a central role in systemic metabolic regulation and immune homeostasis, making it a critical organ in the context of cancer-related inflammation and metastasis.[1 2] In breast cancer, hepatic involvement is common—not only as a metastatic site but also as a target of systemic disruptions driven by the tumor microenvironment, dietary factors, and treatment-induced toxicity.[3] Breast cancer liver metastasis is the third most prevalent site of secondary tumor spread following lymph nodes and bones, and is associated with poor clinical outcomes; median survival for untreated BCLM patients ranges from 4 to 8 months.[4,5] Contributing factors include estrogen receptor negativity, HER2 overexpression, and extensive tumor burden.[6]

Even in the absence of direct metastasis, the liver is vulnerable to inflammation and functional changes due to tumor-secreted cytokines, high-fat diet -induced lipotoxicity, and chemotherapy-associated hepatotoxicity.[7] The hepatic microenvironment—featuring unique sinusoidal architecture, ECM composition, and immune cell populations—can facilitate tumour cell survival, immune evasion, and therapy resistance.[8 9] Changes in hepatic gene expression under such stress conditions may further exacerbate disease progression.

The high-fat diet (HFD) model is widely utilized in experimental research to simulate obesity-induced chronic inflammation, a recognized risk factor for breast cancer development and progression. A diet high in fats promotes systemic inflammation, enhances tumor-promoting cytokines, and contributes significantly to hepatic inflammation and dysfunction associated with cancer. By employing an HFD in combination with DMBA, this study aims to closely replicate the conditions of diet-related oncogenesis and inflammation seen clinically, thereby providing a robust platform for evaluating the therapeutic potential of natural marine-derived compounds such as *Holothuria scabra.*[10]

Two molecular mediators often implicated in this hepatic disruption are nuclear factor kappa B and cysteine-rich angiogenic inducer 61.[7,9] NF-κB is a transcription factor central to pro-inflammatory signalling and cell survival; its aberrant activation has been associated with cancer progression and resistance to apoptosis .[11] CYR61 is a matricellular protein involved in ECM remodeling and angiogenesis, and is linked to tumor aggressiveness and liver fibrosis.[12]

Given the liver's susceptibility to secondary cancer-associated changes, therapeutic strategies aimed at modulating hepatic inflammation and ECM remodeling may offer added value in breast cancer management.[3,13,14] Marine-derived compounds have garnered interest due to their multitarget bioactivity and safety profiles. *Holothuria scabra*, widely used in traditional Asian medicine, is rich in triterpene glycosides, peptides, and polysaccharides with reported anti-inflammatory and anticancer effects.[15,16]

Methanol extract of *H. scabra* has demonstrated promising activity in downregulating IL-6 and NF-κB expression, improving liver histology, and modulating tumor-associated molecular pathways.[17] These findings raise the possibility of its role in suppressing both NF-κB and CYR61 expression in the liver under oncogenic stress.

In this study, we employed a model of DMBA- and HFD-induced breast cancer, which replicates inflammation- and diet-associated carcinogenesis. The primary objective was to investigate the effects of SCME on hepatic expression of NF-κB and CYR61, two key molecular mediators of inflammation and extracellular matrix remodelling in the liver. This research addresses a critical knowledge gap by exploring whether natural marine-derived compounds can counteract hepatic molecular disruptions in cancer-bearing hosts. Understanding the impact of SCME on these gene pathways could reveal novel liver-directed interventions for mitigating systemic inflammatory damage and enhancing therapeutic outcomes in breast cancer. Given the increasing recognition of the liver as both a sentinel and secondary victim in cancer progression, this study is urgent and timely within the context of integrative oncology.

METHODS

This experimental study applied a post-test only control group design based on a randomized complete block design (RCBD). Female C57BL/6J mice aged 10–11 weeks were sourced from a certified breeding facility (iRAT, Indonesia) and acclimatized for one week before the start of the study. Using Federer's formula, the sample size was determined to include five groups of six mice each (n = 30).

The mice were randomly allocated into five groups: (1) a normal diet (ND) group receiving only a standard diet, (2) a positive control group receiving a high-fat diet (HFD) along with 7,12-dimethylbenz[a]anthracene (DMBA) induction, and three treatment groups (T1, T2, and T3) which received HFD, DMBA, and sea cucumber methanol extract (SCME) at doses of 0.33, 0.66, and 0.99 g/kg body weight, respectively. The HFD was provided ad libitum from day 0, and DMBA (1 mg/kg BW, Sigma-Aldrich, USA) was injected subcutaneously into the mammary gland area once per week for six consecutive weeks. Oral administration of SCME began 24 hours after each DMBA injection throughout the induction period. Confirmation of breast cancer development and tumor progression in the animal model was established through histopathological evaluation and tumor burden assessment as previously confirmed by histopathological assessment in Ratnawati et al. (2024).[10]

The SCME was prepared from *Holothuria scabra* specimens collected in Gresik, East Java, Indonesia. After the removal of internal organs, the sea cucumbers were frozen at −80°C, sliced, and macerated in methanol at a ratio of 1:3 (w/v) for 24 hours at room temperature. The solution was filtered with Whatman No. 1 paper, and the methanol was evaporated under reduced pressure using a rotary evaporator at 40°C. The resulting crude extract was

JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i5.50957
JKD (DMJ), Volume 14, Number 5, September 2025 : 247-253

stored at −20°C until use. Previous phytochemical analyses of Holothuria scabra methanol extract (SCME) identified bioactive compounds including triterpene glycosides, sulfated polysaccharides, and peptides. [18]These compounds have been associated with anti-inflammatory and anticancer properties, potentially mediating the observed NF-κB and CYR61 suppression.

At day 62, all animals were euthanized, and their livers were collected, snap-frozen in liquid nitrogen, and stored at −80°C. Total RNA was isolated from 50–100 mg of liver tissue using GENEzol™ Reagent (Geneaid, Taiwan) according to the manufacturer's instructions. RNA yield and purity were assessed spectrophotometrically using a NanoDrop™ (Thermo Scientific, USA).

Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using the MyTaq™ One-Step RT-PCR Kit (Bioline, UK). Expression of NF-κB, CYR61, and the reference gene GAPDH was analyzed using gene-specific primers. The following primer sequences were used: GAPDH (Forward: 5′-TTGATGGCAACAATCTCCAC-3′, Reverse: 5′-CGTCCCGTAGACAAAATGGT-3′), NF-κB (Forward: 5′-GGCCGGAAGACCTATCCTACT-3′, Reverse: 5′-CTACAGACACAGCGCACACT-3′), and CYR61 (Forward: 5′-GATGACCTCCTCGGACTCGAT-3′, Reverse: 5′ CGTGCAGAGGGTTGAAAAGAA-3′). The PCR conditions included a 30-minute reverse transcription step at 50°C, an initial denaturation at 95°C for 1 minute, followed by 35 cycles of denaturation at 95°C for 15 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute.

PCR products were separated using 2% agarose gel electrophoresis stained with SYBR™ Safe DNA Gel Stain (Invitrogen, USA) and visualized under a BluePad LED transilluminator. Band intensity was quantified using ImageJ software, and gene expression levels of NF-κB and CYR61 were normalized against GAPDH as the internal control.

Statistical analysis was conducted using SPSS version 25. One-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc test was performed to compare differences among groups. A p-value of less than 0.05 was considered statistically significant. Graphs were created using GraphPad Prism version 8.0.

RESULTS

Effect of SCME on Hepatic NF-κB Gene Expression

The expression level of the NF-κB gene in liver tissues was significantly elevated in the HFD + DMBA (positive control) group compared to the normal diet (ND) group (1.46 ± 0.94 vs. 0.67 ± 0.15, $p < 0.001$). Treatment with SCME resulted in a dose-dependent reduction in NF-κB expression. At doses of 0.33, 0.66, and 0.99 g/kg BW, the expression levels were 1.20 ± 0.15, 0.98 ± 0.076, and 0.82 ± 0.17, respectively. Notably, the highest dose (T3) significantly reduced NF-κB expression compared to the HFD + DMBA group ($p < 0.05$), approaching values seen in the ND group. However, the reductions observed in the T1 and T2 groups were not statistically different from each other (Fig. 1 and 2)

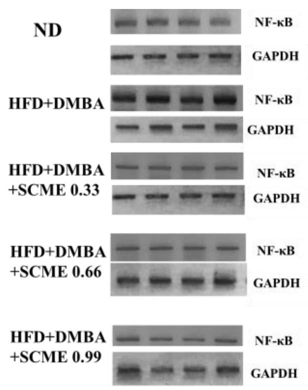

Figure 1. Representative gel electrophoresis images showing hepatic NF-κB and GAPDH mRNA expression levels in mice from each experimental group (only 4 representative samples shown). The upper band in each set corresponds to NF-κB, while the lower band corresponds to GAPDH as control.

JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i5.50957
JKD (DMJ), Volume 14, Number 5, September 2025 : 247-253

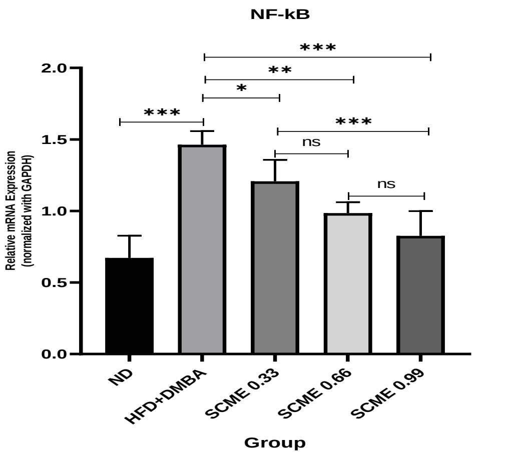

Figure 2. Post Hoc Test Results for NF-κB Gene Expression. ND = Normal Diet, HFD = High Fat Diet, SCME = Sea Cucumber Methanol Extract. Post Hoc Test: * = Significant, ** = Highly Significant, ns = Not Significant.

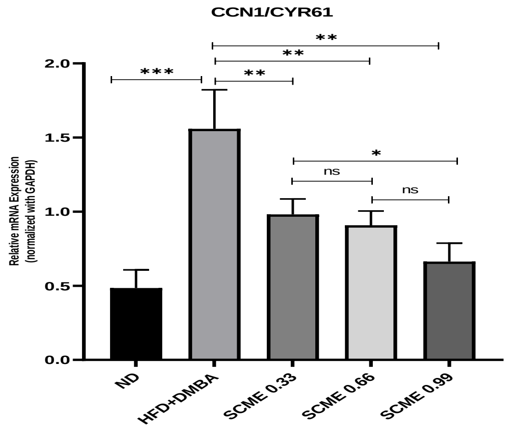

Figure 4. Post Hoc Test Results for CYR61 Gene Expression. ND = Normal Diet, HFD = High Fat Diet, SCME = Sea Cucumber Methanol Extract. Post Hoc Test: * = Significant, ** = Highly Significant, ns = Not Significant.

Effect of SCME on Hepatic CYR61 Gene Expression

Similarly, CYR61 gene expression in the liver was significantly upregulated in the HFD + DMBA group (1.55 ± 0.26) compared to the ND group (0.48 ± 0.12, $p < 0.001$). SCME treatment led to a dose-dependent downregulation of CYR61, with mean expression levels of 0.98 ± 0.103 (T1), 0.90 ± 0.096 (T2), and 0.66 ± 0.12 (T3). The T3 group exhibited a statistically significant decrease in CYR61 expression relative to the HFD + DMBA group ($p < 0.05$), although T1 and T2 showed no significant differences between each other (Fig. 3 and 4)

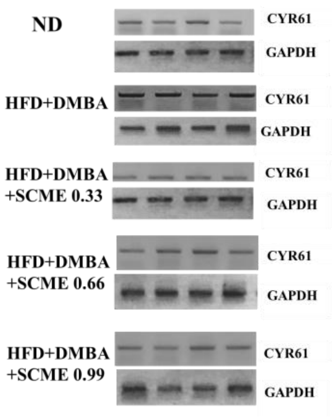

Figure 3. Representative gel electrophoresis images showing hepatic CYR61 and GAPDH mRNA expression levels in mice from each experimental group (n = 5 per group, 3 representative samples shown). The upper band in each set corresponds to CYR61, and the lower band represents GAPDH as the internal control.

DISCUSSION

The present study demonstrates that methanol extract of Holothuria scabra (SCME) significantly reduces hepatic NF-κB and CYR61 gene expression in a breast cancer mouse model induced by a high-fat diet (HFD) and DMBA. These findings provide crucial molecular evidence supporting SCME's therapeutic potential in mitigating inflammation and fibrosis signaling pathways commonly implicated in breast cancer-associated liver complications.

Breast cancer commonly metastasizes to the liver, making hepatic tissue particularly vulnerable to systemic inflammatory stress and metabolic dysregulation driven by tumor progression. Preclinical studies consistently highlight hepatic inflammation and extracellular matrix remodeling as early indicators in breast cancer pathology, linked to cytokine release, lipid dysmetabolism, and endocrine disruption. [19] [20] Elevated NF-κB activity is one of the key mediators in this systemic inflammatory milieu.[21] [22] Our data aligns with previous findings that show persistent activation of NF-κB in liver tissues during tumor progression and suggest that SCME exerts anti-inflammatory effects by suppressing NF-κB transcriptional activity in hepatic cells.

The dose-dependent reduction of NF-κB expression in the liver after SCME administration supports the notion that *H. scabra* extract may interrupt upstream inflammatory cascades, possibly through inhibition of IL-6 signaling and IκBα degradation, as suggested by other studies.[18,23] This is particularly relevant considering that IL-6 is a known inducer of NF-κB, and that both IL-6 and NF-κB are central to cancer-associated inflammation.

This study demonstrated a significant downregulation of hepatic CYR61 gene expression following treatment with *Holothuria scabra* methanol extract (SCME) in a breast cancer mouse model induced by DMBA and a high-fat diet. CYR61, a matricellular protein known to regulate extracellular matrix (ECM) remodeling, angiogenesis, and metastasis, is often overexpressed in aggressive breast cancer subtypes, including triple-negative breast cancer. Its suppression suggests that SCME may influence molecular pathways involved in tumor-associated liver remodeling.

Although the detailed molecular mechanisms remain to be elucidated, previous studies have implicated several signaling pathways—such as TGF-β, Wnt/β-catenin, and PI3K/AKT—in regulating CYR61 expression.[24] It is plausible that SCME interferes with one or more of these regulatory axes, resulting in attenuated CYR61 transcription. Supporting this hypothesis, compounds identified in *H. scabra*, including triterpene glycosides, sulfated polysaccharides, and saponins, have shown potential anticancer activities in preclinical studies. Molecular docking analyses have further demonstrated that bioactive components such as holothurin A and 24-dehydroechinoside exhibit affinity for breast cancer-related molecular targets, including NF-κB-associated sites.[18,25,26]

Unlike previous studies that reported histopathological improvements in the liver following marine-derived compound administration [27 28] , our investigation focused specifically on gene expression without histological assessment. Nevertheless, the significant modulation of CYR61 and NF-κB expression observed here provides strong molecular evidence of SCME's hepatic activity in the context of cancer-induced inflammation.

Additional marine-derived molecules such as comaparvin and echinoside B have also been shown to inhibit NF-κB activation and tumor growth in vivo, offering comparative insight into the therapeutic potential of *H. scabra*. These findings highlight the promise of marine biocompounds in modulating oncogenic and inflammatory pathways.

Nevertheless, this study has several limitations. Primarily, reliance on semi-quantitative RT-PCR alone restricts comprehensive understanding at the protein level. To address this, subsequent studies should include quantitative protein analyses such as western blotting or ELISA to validate gene expression findings. Moreover, the absence of biochemical liver function tests (e.g., AST and ALT) and serum cytokine profiles in this study limits our conclusions regarding SCME's systemic anti-inflammatory effects and hepatic protective properties.

Future studies should investigate the specific molecular pathways targeted by SCME, possibly including upstream regulators of NF-κB and CYR61 such as STAT3, AKT, and MAPK. Proteomic analysis, receptor-binding assays, and the use of knockout models would strengthen the mechanistic understanding.

In summary, this study confirms that methanol extract of *Holothuria scabra* downregulates NF-κB and CYR61 gene expression in the liver of breast cancer mice, suggesting its potential as a dual anti-inflammatory and antifibrotic agent. These findings provide a rationale for further investigation of *H. scabra* as a supportive therapeutic in breast cancer, especially in patients at risk for hepatic comorbidities.

CONCLUSION

This study confirms that *Holothuria scabra* methanol extract (SCME) significantly downregulates hepatic NF-κB and CYR61 gene expression in a breast cancer mouse model induced by high-fat diet and DMBA. These findings suggest SCME's potential as a dual anti-inflammatory and antifibrotic agent, supporting its role as a complementary approach in breast cancer management. Further research is needed to clarify its mechanisms and clinical relevance.

ETHICAL APPROVAL

All experimental protocols were approved by the Research Ethics Committee of Universitas Kristen Maranatha (Ethical Clearance No.: 112/KEP/V/2021).

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research was funded by the Research and Community Service Institute (LPPM) of Maranatha

Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i5.50957
JKD (DMJ), Volume 14, Number 5, September 2025 : 247-253

Christian University through the Skema B Research Grant Scheme.

AUTHOR CONTRIBUTIONS

D.C.M. conceptualized the study, supervised the research process, and prepared the original manuscript draft. R.G.S. contributed to data curation, formal analysis, and methodology development. H.R. conducted the histological examinations and contributed to the interpretation of liver tissue results. T.L.W. assisted in the pathological analysis and critically reviewed the manuscript. A.S. performed data validation. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Research and Community Service Institute (LPPM) of Maranatha Christian University for funding support. We also extend our sincere thanks to the Maranatha Biomelecular Laboratory for providing the facilities and technical assistance essential for this study.

REFERENCES

1. Gan C, Yuan Y, Shen H, et al. Liver diseases: epidemiology, causes, trends and predictions. Signal Transduction and Targeted Therapy 2025;10(1):33. DOI: 10.1038/s41392-024-02072-z.
2. Ma X, Huang T, Chen X, et al. Molecular mechanisms in liver repair and regeneration: from physiology to therapeutics. Signal Transduction and Targeted Therapy 2025;10(1):63. DOI: 10.1038/s41392-024-02104-8.
3. Leser C, Dorffner G, Marhold M, et al. Liver function indicators in patients with breast cancer before and after detection of hepatic metastases-a retrospective study. PLoS One 2023;18(3):e0278454. (In eng). DOI: 10.1371/journal.pone.0278454.
4. Rashid NS, Grible JM, Clevenger CV, Harrell JC. Breast cancer liver metastasis: current and future treatment approaches. Clin Exp Metastasis 2021;38(3):263–277. (In eng). DOI: 10.1007/s10585-021-10080-4.
5. Zou X, Zou H-L, Luo X, et al. Retrospective comparative survival analysis of ablation plus systemic therapy versus systemic therapy alone for breast cancer liver metastases, stratified by extrahepatic metastases status. The Breast 2025;79:103876. DOI: https://doi.org/10.1016/j.breast.2025.103876.
6. Pegram M, Jackisch C, Johnston SRD. Estrogen/HER2 receptor crosstalk in breast cancer: combination therapies to improve outcomes for patients with hormone receptor-positive/HER2-positive breast cancer. NPJ Breast Cancer 2023;9(1):45. (In eng). DOI: 10.1038/s41523-023-00533-2.
7. Bril F, Elbert A. Metabolic dysfunction-associated steatotic liver disease and urinary system cancers: Mere coincidence or reason for concern? Metabolism 2024;162:156066. DOI: 10.1016/j.metabol.2024.156066.
8. Ye H, Minhajuddin M, Krug A, et al. The Hepatic Microenvironment Uniquely Protects Leukemia Cells through Induction of Growth and Survival Pathways Mediated by LIPG. Cancer Discov 2021;11(2):500–519. (In eng). DOI: 10.1158/2159-8290.Cd-20-0318.
9. Zhao M, Huang H, He F, Fu X. Current insights into the hepatic microenvironment and advances in immunotherapy for hepatocellular carcinoma. Frontiers in Immunology 2023;Volume 14 - 2023 (Review) (In English). DOI: 10.3389/fimmu.2023.1188277.
10. Ratnawati H, Wargasetia TL, Larissa L, Alvitri L, Bryant K. HOLOTHURIA SCABRA METHANOL EXTRACT INHIBITS CANCER GROWTH THROUGH TGF-beta/PI3K/PTEN SIGNALING PATHWAY IN BREAST CANCER MICE MODEL. Exp Oncol 2024;46(1):22–29. DOI: 10.15407/exp-oncology.2024.01.022.
11. Guo Q, Jin Y, Chen X, et al. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduction and Targeted Therapy 2024;9(1):53. DOI: 10.1038/s41392-024-01757-9.
12. Yang R, Chen Y, Chen D. Biological functions and role of CCN1/Cyr61 in embryogenesis and tumorigenesis in the female reproductive system (Review). Mol Med Rep 2018;17(1):3–10. DOI: 10.3892/mmr.2017.7880.
13. Huang J, Zhang L, Wan D, et al. Extracellular matrix and its therapeutic potential for cancer

JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i5.50957
JKD (DMJ), Volume 14, Number 5, September 2025 : 247-253

treatment. Signal Transduction and Targeted Therapy 2021;6(1):153. DOI: 10.1038/s41392-021-00544-0.
14. Roy AM, Iyer R, Chakraborty S. The extracellular matrix in hepatocellular carcinoma: Mechanisms and therapeutic vulnerability. Cell Reports Medicine 2023;4(9):101170. DOI: https://doi.org/10.1016/j.xcrm.2023.101170.
15. Hossain A, Dave D, Shahidi F. Antioxidant Potential of Sea Cucumbers and Their Beneficial Effects on Human Health. Mar Drugs 2022;20(8) (In eng). DOI: 10.3390/md20080521.
16. Jattujan P, Chalorak P, Siangcham T, et al. Holothuria scabra extracts possess anti-oxidant activity and promote stress resistance and lifespan extension in Caenorhabditis elegans. Experimental Gerontology 2018;110:158–171. DOI: https://doi.org/10.1016/j.exger.2018.06.006.
17. Liliana Wargasetia T, Ratnawati* H, Kinghua Liana L, Larissa L, Valencia Imannuel E. Holothuria scabra Extract Improves Histopathological Features and Inhibits Cancer Growth Through IL-6 and NF-κB Signaling Pathways in Breast Cancer Mice Model. Research Journal of Pharmacognosy 2024;11(2):1–9. DOI: 10.22127/rjp.2023.417833.2233.
18. Wargasetia TL, Ratnawati H, Liana LK, Larissa L, Imannuel EV. Holothuria scabra Extract Improves Histopathological Features and Inhibits Cancer Growth Through IL-6 and NF-κB Signaling Pathways in Breast Cancer Mice Model. Research Journal of Pharmacognosy 2024;11(2):1–9. (Article). DOI: 10.22127/RJP.2023.417833.2233.
19. Banerjee P, Gaddam N, Chandler V, Chakraborty S. Oxidative Stress–Induced Liver Damage and Remodeling of the Liver Vasculature. The American Journal of Pathology 2023;193(10):1400–1414. DOI: https://doi.org/10.1016/j.ajpath.2023.06.002.
20. Zhao H, Wu L, Yan G, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6(1):263. (In eng). DOI: 10.1038/s41392-021-00658-5.
21. Nejak-Bowen K, Kikuchi A, Monga SP. Beta-catenin-NF-κB interactions in murine hepatocytes: a complex to die for. Hepatology 2013;57(2):763–74. (In eng). DOI: 10.1002/hep.26042.
22. Huang L, Zhao Z, Duan C, et al. Lactobacillus plantarum C88 protects against aflatoxin B1-induced liver injury in mice via inhibition of NF-κB–mediated inflammatory responses and excessive apoptosis. BMC Microbiology 2019;19(1):170. DOI: 10.1186/s12866-019-1525-4.
23. Zhang KW, Wang D, Cai H, et al. IL-6 plays a crucial role in epithelial-mesenchymal transition and pro-metastasis induced by sorafenib in liver cancer. Oncology Reports 2021;45(3) (Article). DOI: 10.3892/or.2021.7926.
24. Zhang C, Wei W, Tu S, et al. Upregulation of CYR61 by TGF-β and YAP signaling exerts a counter-suppression of hepatocellular carcinoma. Journal of Biological Chemistry 2024;300(4). DOI: 10.1016/j.jbc.2024.107208.
25. Wargasetia TL. Mechanisms of cancer cell killing by sea cucumber-derived compounds. Investigational New Drugs 2017;35(6):820–826. (Review). DOI: 10.1007/s10637-017-0505-5.
26. Wargasetia TL, Liana LK, Widodo N, Annisa Y, Hermanto FE. Extract of Holothuria scabra exhibits synergistic effect with chemotherapeutic agents against breast cancer in vitro. Journal of Pharmacy and Pharmacognosy Research 2025;13(3):919–924. (Article). DOI: 10.56499/jppres24.2069_13.3.919.
27. Wei Q, Guo JS. Developing natural marine products for treating liver diseases. World J Clin Cases 2022;10(8):2369–2381. (In eng). DOI: 10.12998/wjcc.v10.i8.2369.
28. Tammam MA, Pereira F, Aly O, et al. Investigating the hepatoprotective potentiality of marine-derived steroids as promising inhibitors of liver fibrosis. RSC Adv 2023;13(39):27477–27490. (In eng). DOI: 10.1039/d3ra04843h