Asian Multidisciplinary Research Journal of Economy and Learning

Volume 2, Issue 7, Page 24 – 31, 2025, Article No. AMJEL 00061
ISSN: 3063-1424

The Effect of Ethanol Extract of Mobe Leaves (*Artocarpus lacucha* Buch-Ham.) on Caspase-3 Expression in Liver Tissue Rats Induced by Carbon Tetrachloride

Meiva Amelia Lubis[++ *1], Indah Pertiwi [2], Damayanti[3]

[1,2] *Faculty of Pharmacy and Health Sciences, Lecturer, Helvetia Institute of Health Sciences, Medan, Indonesia*
[3] *Faculty of Medicine, Dentistry and Health Sciences, Lecturer, Prima Indonesia University, Medan, Indonesia*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
https://doi.org/10.70471/nvgf9h70

Original Research Article

Received: 16/07/2025
Accepted: 30/07/2025
Published: 31/07/2025

Abstract

Carbon tetrachloride (CCl_4) is a commonly used hepatotoxic agent to induce liver injury via oxidative stress and the activation of hepatocyte apoptosis. One hallmark of apoptosis is the increased expression of Caspase-3, a key executor enzyme in the programmed cell death pathway. The ethanol extract of Mobe leaves (*Artocarpus lacucha* Buch-Ham.) is known to contain bioactive compounds such as flavonoids and triterpenoids, which have demonstrated hepatoprotective potential. This study investigates the hepatoprotective effects of ethanol extract of Mobe leaves (EEML) on Caspase-3 expression in the liver tissues of rats induced by carbon tetrachloride. This experimental study utilized 30 male rats randomly assigned into six groups. The negative control group received CCl_4 - and

[++] *Indonesia;*
**Corresponding author: Email: meivalubis@helvetia.ac.id*
Cite as: Lubis, M. A., Pertiwi, I., & Damayanti. (2025). The Effect of Ethanol Extract of Mobe Leaves (Artocarpus lacucha Buch-Ham.) on Caspase-3 Expression in Liver Tissue Rats Induced by Carbon Tetrachloride. Asian Multidisciplinary Research Journal of Economy and Learning, 2(7), 24–30.
https://doi.org/10.70471/nvgf9h70

CMC-Na 1%, while the positive control group received silymarin and CCl_4. Four treatment groups received oral doses of EEML at 50, 100, 200, and 400 mg/kg body weight for 15 days with CCl_4 induction. Caspase-3 expression in liver tissue was analyzed using the immunohistochemistry (IHC) method and quantified based on the number of positively stained cells across five microscopic fields. The results showed a significant reduction in Caspase-3 expression ($p<0.05$) in the EEML-treated groups compared to the negative control, with the 400 mg/kg dose achieving an effect comparable to silymarin. These findings suggest that EEML possesses hepatoprotective properties through apoptosis inhibition, evidenced by decreased Caspase-3 expression in CCl_4 injured liver tissue.

Keywords: *Artocarpus lacucha, hepatoprotection, Caspase-3, apoptosis, Carbon tetrachloride, immunohistochemistry.*

1. INTRODUCTION

The liver is a vital organ responsible for numerous metabolic functions, including detoxification, protein synthesis, and energy storage. Impairment of liver function can lead to severe complications such as cirrhosis and acute liver failure, which significantly affect quality of life and mortality. One of the primary causes of liver injury is exposure to hepatotoxic compounds, such as carbon tetrachloride (CCl_4), which is widely used in experimental models to study oxidative stress and lipid peroxidation (Basu, 2011; Bernal & Wendon, 2013). Therefore, experimental studies on hepatoprotective agents are crucial for developing safe and effective therapeutic alternatives.

CCl_4 is a lipophilic compound capable of penetrating hepatic cell membranes, where it undergoes biotransformation in the endoplasmic reticulum by cytochrome P450 enzymes, generating reactive radicals such as trichloromethyl (CCl_3•) and trichloromethyl peroxyl (CCl_3OO•). These radicals induce oxidative stress, causing DNA damage and activating apoptotic signaling through the mitochondrial pathway. Apoptosis in hepatocytes is marked by elevated Caspase-3 expression, a critical executioner of programmed cell death (Lawrence, 2009; Liu et al., 2017). Hence, inhibiting Caspase-3 activation may represent a promising therapeutic approach in preventing liver disease progression.

One preventative strategy against liver damage involves the use of natural products with antioxidant and anti-apoptotic properties. Herbal extracts have long been used in traditional medicine to treat liver dysfunction, as referenced in the Materia Medika Indonesia (Depkes RI, 1995). Artocarpus lacucha Buch-Ham., commonly known as Mobe in Indonesia, is one such medicinal plant traditionally utilized for its therapeutic properties. It contains flavonoids, tannins, saponins, and phenolic compounds known for their biological activity (Gautam & Patel, 2014).

Previous research has demonstrated that ethanol extract of Mobe leaves exhibits strong antioxidant activity. Using the ABTS assay, the extract showed an IC_{50} value of 87.5 µg/mL, categorizing it as a potent antioxidant (Pulungan, 2018; Martysiak et al., 2011). In addition to its antioxidative properties, extract of Mobe Leaves also possesses anti-apoptotic effects, potentially reducing the expression of apoptotic enzymes such as Caspase-3 (Hari et al., 2014). Thus, evaluating Caspase-3 expression serves as a direct measure of the anti-apoptotic effects of the extract.

The Wistar rat model induced with CCl_4 is a widely accepted experimental method for assessing hepatoprotective agents. These animals respond predictably to hepatotoxins and are suitable for biochemical and histological analyses. Immunohistochemistry (IHC) serves as an essential technique to detect specific protein expression, such as Caspase-3, in liver tissue. This method provides a molecular-level insight into apoptosis activity following exposure to hepatotoxins or therapeutic intervention (Rosida, 2016).

Silymarin, a bioactive compound derived from milk thistle (Silybum marianum), is commonly used as a positive control in hepatoprotective studies due to its well-documented antioxidant, antifibrotic, and antiproliferative effects (Javed et al., 2011; Siegel & Stebbing, 2013). Using Silymarin as a comparator allows for objective assessment of hepatoprotective effect of Mobe leaf extract. Monitoring Caspase-3 expression offers a

clear, molecular based measure of hepatocyte apoptosis and thus enables evaluation of therapeutic efficacy with high specificity.

Given this background, the present study aims to evaluate the effects of ethanol extract of Mobe leaves (Artocarpus lacucha Buch-Ham.) on Caspase-3 expression in the liver tissue of rats induced by carbon tetrachloride. This research is expected to contribute to the scientific validation of Mobe leaves as a potential hepatoprotective agent, particularly in modulating apoptosis pathways. Furthermore, the study promotes the utilization of indigenous medicinal plants as complementary therapies in liver disorders, paving the way for the development of standardized herbal medicines in the future.

2. METHODS

2.1 Research Design and Approach

This study employed a quantitative experimental laboratory approach with a post-test only control group design. The primary objective of this design was to determine the effect of ethanol extract of Mobe leaves (EEML) on Caspase-3 expression in liver tissue of rats induced with carbon tetrachloride (CCl_4). It is classified as a true experimental study, as it involved a negative control group, a positive control group, and multiple treatment groups assigned randomly (randomized control). The independent variable in this study was the administration of ethanol extract of Mobe leaves, while the dependent variable was the expression of Caspase-3 in liver tissue of rats.

2.2 Study Location and Period

The research was conducted at three facilities: the Biology Laboratory of the Faculty of Pharmacy, Universitas Sumatera Utara; the Histology Laboratory of the Faculty of Medicine, Universitas Sumatera Utara; and the Anatomical Pathology Laboratory of the Teaching Hospital at Universitas Sumatera Utara. The experimental procedures and data collection were carried out throughout the year 2024.

2.3 Population and Sample

The study population consisted of male Wistar strain white rats (Rattus norvegicus) weighing between 150–200 grams and aged 2–3 months. The sampling technique used was purposive sampling, based on predetermined inclusion and exclusion criteria. A total of 30 rats were randomly divided into six groups, each consisting of five animals:

- Group I: EEML 400 mg/kg BW + CCl_4
- Group II: EEML 200 mg/kg BW + CCl_4
- Group III: EEML 100 mg/kg BW + CCl_4
- Group IV: EEML 50 mg/kg BW + CCl_4
- Group V: Positive control (Silymarin 100 mg/kg BW + CCl_4)
- Group VI: Negative control (CMC-Na 1% + CCl_4)

2.4 Treatment and Hepatotoxic Induction

The ethanol extract of Mobe leaves was administered orally via gavage once daily for 14 days. Carbon tetrachloride (CCl_4) induction was performed intraperitoneally on days 7 and 14 at a dose of 1 mL/kg body weight, diluted in olive oil at a 1:1 ratio. The selection of EEML doses was based on preliminary studies and relevant literature (Pulungan, 2018; Hari et al., 2014). Silymarin, serving as the positive control, was also administered orally over the 14-day treatment period.

2.5 Data Analysis

Data analysis was carried out using both qualitative and quantitative descriptive approaches based on the results of immunohistochemical (IHC) staining for Caspase-3 expression in rat liver tissue. Caspase-3 positive expression was identified by brown staining in the nuclei of hepatocytes, whereas cells lacking expression remained unstained. The number of cells expressing and not expressing Caspase-3 was manually counted using a light microscope at 400x magnification. As this study primarily focused on visual

observations of protein expression through IHC, inferential statistical analysis was not performed.

The results were presented in the form of frequency tables and photomicrograph images, which were compared across all treatment groups to evaluate the inhibitory effect of Mobe leaf extract on Caspase-3 expression. Assessments were conducted by two independent observers to ensure consistency and objectivity of visual interpretation. The interpretation of findings was based on the visual trend of reduced Caspase-3 expression in treatment groups compared to the negative control group.

3. RESULTS AND DISCUSSIONS

3.1 Treatment and Induction Process

This study utilized male Wistar rats as the animal model to evaluate the hepatoprotective effect of the ethanol extract of Mobe leaves (EEML) against Caspase-3 protein expression, which plays a critical role in hepatocyte apoptosis. The animals were housed under standard laboratory conditions with adherence to ethical and welfare protocols and were provided with food and water ad libitum.

The experimental animals were divided into six groups, each consisting of five rats. The normal control group received only CMC-Na 1%. The negative control group was administered CMC-Na 1% along with CCl_4 at 1 mL/kg BW. The positive control group received 100 mg/kg BW of silymarin. The treatment groups were administered EEML at escalating doses of 50, 100, 200, and 400 mg/kg BW, followed by CCl_4 induction at 1 mL/kg BW via intraperitoneal injection on days 7 and 14.

The animals were sacrificed using intraperitoneal ketamine injection (0.2 mL). Rats were placed in a supine position, and the abdominal skin was incised and sterilized with 70% ethanol. Liver tissues were excised, rinsed with 0.9% NaCl to remove connective tissues, and transferred into Petri dishes for macroscopic observation and weighing. The samples were then fixed in 10% neutral buffered formalin (NBF), processed into paraffin blocks, and subjected to immunohistochemistry (IHC) staining. Caspase-3 expression was visualized by brown staining—ranging from dark brown, medium brown, to light purplish-brown—while non-expressing cells remained purple.

Microscopic examination was performed using IHC staining to assess cell proliferation via the mAgNOR parameter, with expression observed in 200 cells per sample across five different fields of view per slide (Pratiwi, 2010).

3.2 Mechanism of CCl_4-Induced Hepatotoxicity

Carbon tetrachloride (CCl_4) is a widely used chemical in toxicological studies for inducing hepatotoxicity in animal models. Its hepatotoxic mechanism relies heavily on hepatic bioactivation via the cytochrome P450 enzyme system, especially the CYP2E1 isoform, which converts CCl_4 into trichloromethyl radicals ($\bullet CCl_3$) (Basu, 2011). These highly reactive radicals exhibit strong affinity for lipid structures within hepatocyte membranes, initiating lipid peroxidation and disrupting cellular membrane integrity.

The $\bullet CCl_3$ radicals can also react with oxygen to form trichloromethyl peroxyl radicals ($\bullet CCl_3O_2$), which exacerbate oxidative damage within hepatocytes. The accumulation of lipid peroxidation impairs the integrity of organelles such as mitochondria and the endoplasmic reticulum, both vital for hepatic metabolism (Navarro & Senior, 2006). This damage subsequently triggers the release of liver enzymes such as SGOT and SGPT into the serum, which serve as clinical biomarkers of hepatocellular injury (Rosida, 2016). The overall toxic effect initiates acute inflammation and results in both apoptotic and necrotic cell death.

At the molecular level, CCl_4-induced oxidative stress activates inflammatory signaling pathways, including the nuclear factor kappa B (NF-κB), leading to the upregulation of pro-

inflammatory cytokines such as TNF-α and IL-6 (Liu et al., 2017; Lawrence, 2009). These cytokines accelerate liver damage by amplifying maladaptive immune responses. Concurrently, oxidative DNA damage and mitochondrial dysfunction trigger the intrinsic

apoptotic pathway, notably via the activation of Caspase-3, a key executor protein of apoptosis (Kumar et al., 2014). This model thus serves as a valid platform for assessing the hepatoprotective potential of herbal compounds such as EEML.

3.3 Immunohistochemistry: Principle and Relevance

Immunohistochemistry (IHC) is a crucial technique in molecular pathology that combines immunological and histological methods to detect specific proteins in tissue samples. In this study, IHC was utilized to identify Caspase-3 expression in liver tissues of CCl_4-induced rats. The method involved the use of primary antibodies specific to Caspase-3, followed by secondary antibodies conjugated with peroxidase enzymes. Upon application of chromogenic substrates like DAB (diaminobenzidine), a brown coloration appears at the site of antigen expression (Chodidjah & Utari, 2007).

IHC offers not only qualitative identification of target proteins but also insight into their intensity and distribution within the tissue architecture. This is essential for evaluating tissue damage or protection following treatment. In liver tissues exposed to CCl_4, increased Caspase-3 expression indicates apoptosis, which is visibly identifiable through staining. Conversely, reduced numbers of Caspase-3-positive cells following hepatoprotective treatment, such as EEML administration, suggest an anti-apoptotic protective effect.

The relevance of IHC in this study is high, as Caspase-3 is a sensitive molecular indicator of oxidative stress and hepatic inflammation. Visualizing Caspase-3 expression provides direct evidence of the test compound's efficacy in suppressing apoptotic pathways. Moreover, the method strengthens the study's validity by offering a tangible correlation between treatment, histological changes, and molecular response, making IHC an indispensable diagnostic and evaluative tool in hepatoprotective research.

3.4 Caspase-3 Expression Evaluation Results

Table 1. Respondent Characteristics by Age

Treatment Group	Caspase-3 Positive	Caspase-3 Negative
EEML 400 mg/kg BW + CCl_4	71	129
EEML 200 mg/kg BW + CCl_4	86	114
EEML 100 mg/kg BW + CCl_4	95	105
EEML 50 mg/kg BW + CCl_4	102	98
Silymarin 100 mg/kg BW + CCl_4	66	134
CMC-Na 1% + CCl_4	121	79

3.5 Immunohistochemistry: Principle and Relevance

The negative control group, which received CCl_4 and Na-CMC, exhibited the highest number of Caspase-3-positive cells (121), indicating significant hepatocellular apoptosis induced by CCl_4. This confirms that CCl_4 substantially activates apoptosis pathways via oxidative stress and lipid peroxidation (Basu, 2011). The high Caspase-3 expression implies that apoptosis was the predominant cell death mechanism in this hepatotoxicity model.

In contrast, the group treated with 100 mg/kg BW of silymarin—a well-known natural hepatoprotective agent—showed the lowest Caspase-3 expression (66 positive cells). This supports existing evidence that silymarin exerts anti-apoptotic effects by inhibiting reactive oxygen species (ROS) and stabilizing mitochondrial membranes (Surai, 2015; Anton et al., 2020). Silymarin is also known to suppress pro-inflammatory cytokines like TNF-α and IL-6, which are early activators of the extrinsic apoptosis pathway (Vallabhapurapu & Karin, 2009).

In the group treated with 400 mg/kg BW of EEML, Caspase-3 expression decreased to 71 positive cells, approaching the efficacy of silymarin. This indicates that high-dose EEML exhibits strong hepatoprotective activity by significantly suppressing Caspase-3 activation.

This effect is likely attributed to the antioxidant and anti-inflammatory properties of flavonoids and phenolic compounds found in the extract (Hari et al., 2014; Gautam & Patel, 2014), which enhance endogenous antioxidant enzymes such as SOD and downregulate pro-apoptotic proteins including Caspase-3 and TNF-α.

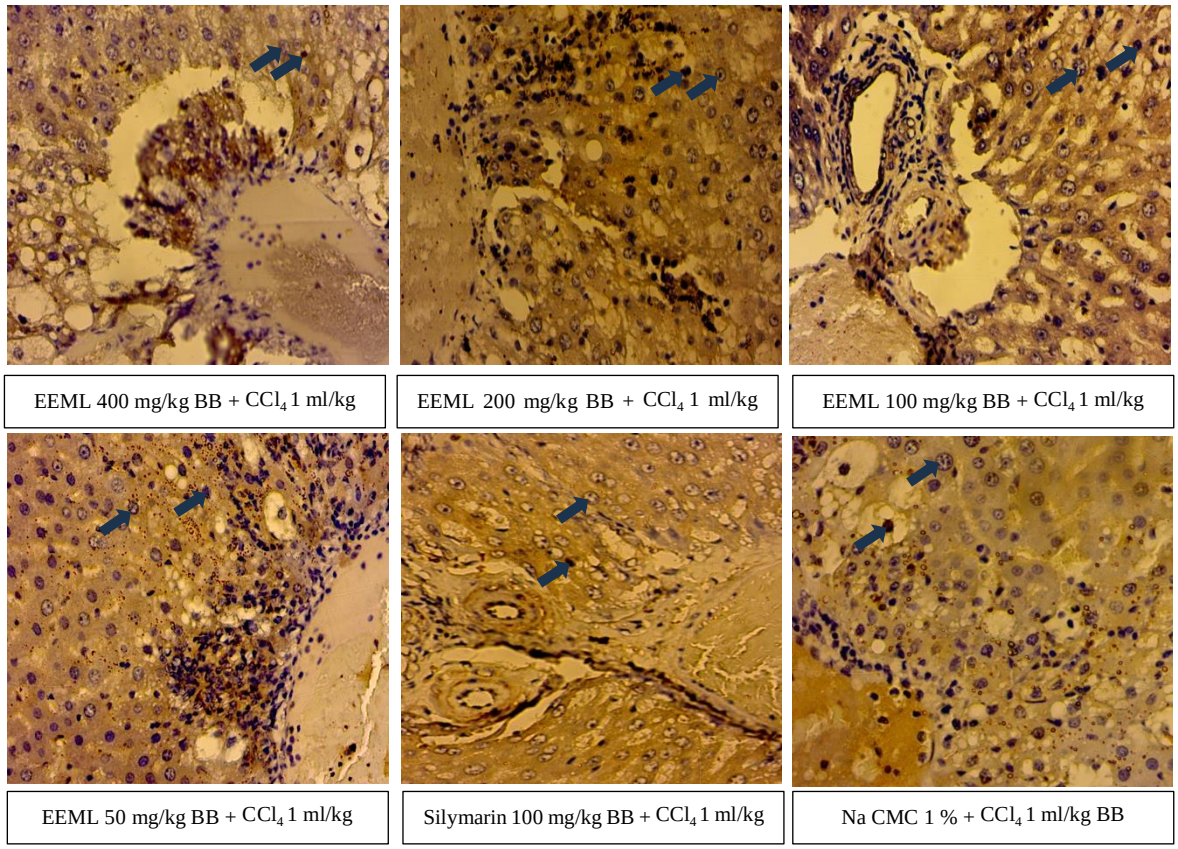
At lower doses (200, 100, and 50 mg/kg BW), Caspase-3-positive cells numbered 86, 95, and 102, respectively. Although these figures show reduced expression compared to the negative control, their inhibitory effect was not as pronounced as the 400 mg/kg BW dose. This suggests a dose-dependent hepatoprotective effect of EEML, wherein its efficacy in suppressing apoptosis increases with higher concentrations. The minimal impact at lower doses may imply insufficient active compound levels to effectively block apoptotic signaling.

Overall, the findings affirm that EEML can inhibit liver cell damage via anti-apoptotic mechanisms, as demonstrated by reduced Caspase-3 expression. This activity is closely linked to the extract's antioxidant compounds intervening in both intrinsic and extrinsic apoptosis pathways. These results support the potential of EEML as a promising natural hepatoprotective candidate, especially at an optimal dose of 400 mg/kg BW and encourage further exploration of its bioactive fractions.

3.6 Immunohistochemistry Visualization

Figure 1 displays photomicrographs of liver tissues stained by IHC. Arrows indicate Caspase-3-positive areas (brown) and negative areas (purple). In the negative control group, Caspase-3 expression was widespread, indicating severe cellular damage. Conversely, the high-dose EEML group showed fewer positive areas, with more localized expression.

Figure 1. Scatterplot for Heteroskedasticity Check



3.7 Role of Antioxidants in Apoptosis Inhibition

The ethanol extract of Mobe leaves (EEDM) is known to contain various bioactive compounds, such as flavonoids, phenolics, and tannins, which exhibit high antioxidant potential (Pulungan, 2018; Hari et al., 2014). Flavonoids play a pivotal role in neutralizing free radicals through ROS scavenging, thereby preventing lipid peroxidation—the initial step in hepatocellular injury. By disrupting oxidative chain reactions, these compounds protect cellular and mitochondrial membranes, which are key points of apoptotic initiation.

The primary molecular mechanism behind the protective effects of flavonoids involves the activation of the Nrf2 (nuclear factor erythroid 2–related factor 2) pathway, a transcription factor that regulates genes encoding endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Nrf2 activation enhances the cell's capacity to eliminate ROS and maintain structural integrity (Surai, 2015). In this context, EEDM acts preventively by upregulating protective proteins while downregulating apoptotic triggers such as Caspase-3 and inflammatory cytokines.

The marked decrease in Caspase-3 expression in EEDM-treated groups, particularly at the 400 mg/kg BW dose, serves as strong evidence of the extract’s anti-apoptotic activity mediated by its antioxidant properties. This indicates that EEDM not only functions as a free radical scavenger but also modulates molecular pathways involved in programmed cell death. By mitigating oxidative stress and suppressing pro-apoptotic protein expression, Mobe leaf extract emerges as a promising therapeutic agent for preventing or attenuating liver injury caused by hepatotoxic agents such as CCl_4 (Huang et al., 2017). This finding also highlights the potential of local medicinal plants as sources of bioactive hepatoprotective agentsThe ethanol extract of Mobe leaves (EEML) is known to contain various bioactive compounds, such as flavonoids, phenolics, and tannins, which exhibit high antioxidant potential (Pulungan, 2018; Hari et al., 2014). Flavonoids play a pivotal role in neutralizing

free radicals through ROS scavenging, thereby preventing lipid peroxidation—the initial step in hepatocellular injury. By disrupting oxidative chain reactions, these compounds protect cellular and mitochondrial membranes, which are key points of apoptotic initiation.

The primary molecular mechanism behind the protective effects of flavonoids involves the activation of the Nrf2 (nuclear factor erythroid 2–related factor 2) pathway, a transcription factor that regulates genes encoding endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Nrf2 activation enhances the cell's capacity to eliminate ROS and maintain structural integrity (Surai, 2015). In this context, EEML acts preventively by upregulating protective proteins while downregulating apoptotic triggers such as Caspase-3 and inflammatory cytokines.

The marked decrease in Caspase-3 expression in EEML-treated groups, particularly at the 400 mg/kg BW dose, serves as strong evidence of the extract’s anti-apoptotic activity mediated by its antioxidant properties. This indicates that EEML not only functions as a free radical scavenger but also modulates molecular pathways involved in programmed cell death. By mitigating oxidative stress and suppressing pro-apoptotic protein expression, Mobe leaf extract emerges as a promising therapeutic agent for preventing or attenuating liver injury caused by hepatotoxic agents such as CCl_4 (Huang et al., 2017). This finding also highlights the potential of local medicinal plants as sources of bioactive hepatoprotective agents.

4. CONCLUSION AND RECOMMENDATIONS

4.1 Conclusion

Based on the findings of this study, it can be concluded that the ethanol extract of Mobe leaves (EEML) exhibits significant hepatoprotective effects against liver damage induced

by carbon tetrachloride (CCl_4), primarily through the inhibition of Caspase-3 protein expression, a key marker of apoptosis. The group of rats treated with EEML at a dose of 400 mg/kg body weight demonstrated a substantial reduction in Caspase-3 expression, comparable to the positive control group treated with silymarin, indicating strong anti-apoptotic activity.

The flavonoid and phenolic content of EEML contributes to its antioxidant properties, effectively neutralizing free radicals, reducing oxidative stress, and inhibiting both intrinsic and extrinsic apoptotic pathways. The use of immunohistochemistry (IHC) as the primary analytical method provided both visual and quantitative evidence of Caspase-3 expression, reinforcing the conclusion that EEML reduces hepatocyte apoptosis. Furthermore, activation of the Nrf2 pathway by active compounds in the extract enhances hepatocellular protection by increasing the expression of endogenous antioxidant enzymes such as SOD, GPx, and catalase.

Therefore, EEML presents a promising natural candidate for adjunctive therapy in cases of hepatotoxicity caused by exposure to toxic chemicals like CCl_4.

4.2 Recommendations

This study recommends the utilization of EEML as a herbal-based hepatoprotective agent, especially at higher doses such as 400 mg/kg body weight, which was found to be the most effective in reducing Caspase-3 expression. For further development, chronic and sub-chronic toxicological studies on EEML should be conducted to ensure its safety for long-term use.

Additionally, further molecular investigations involving pathways such as Nrf2, NF-κB, and p53 are encouraged to broaden our understanding of the biological mechanisms of Mobe leaf extract in relation to different types of liver damage. It is also recommended to develop pharmaceutical formulations of EEML in capsule, tablet, or suspension forms and to conduct clinical trials in humans as a translational step from in vivo findings.

The cultivation and commercialization of Mobe as a pharmaceutical commodity should be promoted by both governmental and academic institutions, given its potential as a high-value natural remedy for hepatotoxicity and other liver diseases.

References

Badan POM RI. (2012). Pedoman teknologi farmasi sediaan berbasis ekstrak. Jakarta: Badan Pengawas Obat dan Makanan Republik Indonesia.

Basu, S. (2011). Carbon tetrachloride-induced hepatotoxicity: A classic model of lipid peroxidation and oxidative stress. Toxicology, 11, 467–480.

Bernal, W., & Wendon, J. (2013). Acute liver failure. The New England Journal of Medicine, 369, 2525–2534.

Chodidjah, E. W., & Utari. (2007). Pengaruh pemberian air rebusan meniran (Phyllanthus niruri Linn) terhadap gambaran histopatologis hati tikus Wistar yang terinduksi CCl_4. Jurnal Anatomi Indonesia, 21(1), 8–12.

Depkes RI. (1995). Materia medika Indonesia (Vol. VI). Jakarta: Departemen Kesehatan Republik Indonesia.

Depkes RI. (2000). Parameter standar umum ekstrak tumbuhan obat. Jakarta: Departemen Kesehatan Republik Indonesia.

Departemen Kesehatan RI. (2007). Pharmaceutical care untuk penyakit hati. Jakarta: Departemen Kesehatan RI.

Gautam, P., & Patel, R. (2014). Artocarpus lakoocha Roxb: An overview. European Journal of Complementary and Alternative Medicine, 1(1), 10–11.

Hari, A., Revikumar, K. G., & Divya, D. (2014). Artocarpus: A review of its phytochemistry and pharmacology. Journal of Pharmacy, 9(1), 7–11.

Huang, W., Ma, K., Zhang, J., & Qiao, H. (2017). The role of Nrf2 in liver disease: Novel molecular mechanisms and therapeutic approaches. Frontiers in Pharmacology, 8, 267.

Kumar, V., Abbas, A., Aster, J., Robbins, S., Cornain, S., & Nasar, I. (2014). Buku ajar patologi Robbins (8th ed.). Jakarta: EGC.

Navarro, V. J., & Senior, J. R. (2006). Drug-related hepatotoxicity. New England Journal of Medicine, 354, 731–739.

Pulungan, W. U. (2018). Aktivitas antioksidan ekstrak n-heksan, etil asetat dan etanol daun mobe (Artocarpus lacucha Buch-Ham.) dengan metode pemerangkapan ABTS. Skripsi, Universitas Sumatera Utara.

Rndsystem. (2004). Caspases. Technical Bulletin. Retrieved from www.rndsystems.com Shinta, D. (2015). Peran Nrf2 dalam regulasi enzim antioksidan. Jurnal Biokimia Indonesia, 11(1), 45–52.

Surai, P. F. (2015). Silymarin as a natural antioxidant: An overview of the current evidence and perspectives. Antioxidants, 4(1), 204–247. https://doi.org/10.3390/antiox4010204