Jurnal Eduhealth
Volume 16, Number 03 2025 DOI 10.54209/eduhealth.v16i03
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

Hepatoprotective Effect of Ethanol Extracted Clove Flower (Syzygium Aromaticum) on Wistar Rat's Hepatocytes Induced by Carbon Tetrachloride (CCl_4)

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Article Info
Keywords:
Carbon tetrachloride,
clove flowers,
hepatocyte

ABSTRACT
Based on WHO, the total death caused only by alcohol causing liver cirrhosis complications was estimated at 637,000 people in 2016. Based on Riskesdas 2018, 3% of Indonesians consumed alcohol 0.3% excessively. One of the liver damage prevention due to alcohol was by consuming plant antioxidants. Ethanol extracted clove flowers (EEBC) contains antioxidant substances such as eugenol and flavonoids which protect hepatocytes from free radicals. The aim of this research was to determine the hepatoprotective effect of ethanol extracted clove flower on hepatocytes induced by carbon tetrachloride (CCl4). Trichloromethyl from CCl4 metabolism by P-450 enzymes caused lipid peroxidation of hepatocyte cell membranes This research was divided into 5 groups with 5 Wistar rats in each group. The group categories were negative control (K1), positive control (K2), 750 mg/KgBW dose EEBC (K3), 875 mg/KgBW dose EEBC (K4), 1000 mg/KgBW dose EEBC (K5). The research procedure was divided into 2 phases. First, administration of extract for 7 days, second, induction of CCl4 on the 8th day. On 9th day, rats were terminated and their livers were taken for histologic preparations. The results showed that K5 had the lesser destruction than positive control but still under negative control, and K3 and K4 almost the same as positive control. In conclusion, ethanol extracted clove flowers had hepatoprotective effect towards hepatocytes of induced CCl4 Wistar rats. Low and moderate doses of EEBC did not have a statistical effect, apparently because the induction of CCl4 was too strong compared to previous studies that used paracetamol.

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INTRODUCTION

The liver is the largest organ in the body, functioning as the first digestive metabolism that food passes through from the digestive tract, which can also synthesize enzymes and detoxify, so that the liver is one of the first organs exposed to substances that are not naturally present in the body and are susceptible to damage. [1,2] According to *the European Association for the Study of the Liver* , the most common liver disease in China is *non-alcoholic fatty liver*

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disease (NAFLD), around 310 million cases, while according to the 2018 Rikesdas, around 0.4% of Indonesia's population suffers from hepatitis. [3,4]

Hepatocytes are one of the cells that are easily damaged by free radicals because of their reactive nature with hepatocyte cell membranes. [5] Examples of free radicals come from carbon tetrachloride (CCl_4), which used to be used in cleaning products. [2] When CCl_4 enters the liver and is metabolized with the help of cytochrome P-450, it will change into *Trichloromethyl* as an active substance that causes damage to the hepatocyte membrane. [5] Damage due to lipid peroxidation follows a microscopic picture in the form of degeneration and intracellular accumulation of hepatocytes, inflammation, cell necrosis, regeneration, and tissue fibrosis. [5] Free radicals can have their toxicity reduced with enzymatic antioxidants and nonenzymatic antioxidants. [2,5]

Antioxidants are substances that can control the level of free radicals in the body and reduce damage to target cells, which can be categorized into natural and synthetic antioxidants, then natural antioxidants are divided into enzymatic and non-enzymatic antioxidants. [6] Enzymatic antioxidants are produced in the body directly in the form of enzymes, while non-enzymatic antioxidants cannot be produced by the body naturally and need to be obtained from foods such as vitamins and plant substances. [6] By mechanism, antioxidants are divided into three groups, namely first-line, second-line, and third-line antioxidants. [6] Flavonoids are the second-line non-enzymatic antioxidants most commonly found in plants and spices in Indonesia such as soybeans, noni fruit, shallots, guava leaves, cinnamon, cashew leaves, and clove flowers. [6–8]

Clove flower is one of the spices that has many functions and is believed to also act as an anti-bacterial, anti-fungal, anti-viral, anti-platelet, anti-cancer, anti-histamine, and antioxidant. [9] Ethanol extract of clove flower contains many active compounds such as eugenol as much as 87%, eugenyl acetate as much as 8.01%, and βcaryophyllene as much as 3.56%. [10] Eugenol has many benefits and can be synthesized into flavone compounds which are known to have very strong antioxidant activity and can protect organs from free radicals in the body. [10]

Ethanol extract of clove flowers that has been studied at a dose of 200 mg/200 grams of mice has a hepatoprotective effect on Wistar strain mice. [11] Other studies also found significant effects in mice induced by clove flower extract at doses of 100 mg, 200 mg and 400 mg per KgBW of mice in the form of increased stimulation of mice with a eugenol base which is thought to increase locomotor activity. [12] This proves that eugenol which is thought to be one of the antioxidants has been proven to have an effect in the study. [12] Unlike previous studies, the author also wants to prove that ethanol extract of clove flowers can act as a preventative, by giving the extract first and then giving free radical induction, in contrast to previous studies where the extract and free radicals were given simultaneously. [11] This study was conducted with the aim of determining the effect of ethanol extract of clove flowers at doses of 750 mg/KgBW, 875 mg/KgBW, and 1000 mg/KgBW as a hepatoprotector in Wistar rats induced by carbon tetrachloride ($CCl4$) microscopically, and to determine the most effective dose for hepatoprotective function.

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MATERIALS AND METHODS

This research was conducted at the Biochemistry and Biomolecular Laboratory of the Faculty of Medicine, General Achmad Yani University, the Animal Laboratory of the Faculty of Medicine, General Achmad Yani University, and the Histology and Pathology Anatomy Laboratory of the Faculty of Medicine, General Achmad Yani University, after obtaining approval from the FK Unjani Ethics Commission with number 004/UH1.07/2021.

Research design: This study is an experimental laboratory study using male *Wistar* rats, with an assessment using a *post-test only control group design* , after the experimental animals were given clove flower ethanol extract orally and then ended with CCl4 induction intraperitoneally on the 8th day.

Object and subject of research: The object of this research is clove flowers from Pengheotan plantation, Cipada, Cisarua, West Bandung Regency, West Java, which have been dried and then extracted using 70% ethanol, stored at a temperature of 2-8 °C. The subjects of this research are male *Wistar rats* obtained from UNPAD and are included in the inclusion criteria, and have been acclimatized for 7 days, divided into one negative control group, one positive control group, and three treatment groups.

Materials and preparation of extracts: Materials for treatment include rat diet and drink, 100% CCl_4, and ethanol extract of clove flowers, while materials for preparation include *xylol solution* , 50%, 80%, 95% alcohol concentration, warm water, dyes (hematoxylin eosin solution, eosin solution), 2% HCl, 2% ammonia, formalin solution, benzol solution, and entelan. The making of clove flower ethanol extract begins with a maceration process using 70% ethanol in two stages. The first stage (75%) is carried out for three days in a closed container and stirred periodically. The second stage (25%) is remaceration, the process of which is the same as the first stage. The resulting macerate is then thickened with *a rotary evaporator* at a temperature of 60 °C so that the extract has a thick concentration. [12]

Determination of dosage and method of administration: Previous studies have found significant effects from ethanol extract of clove flowers at doses of 100 mg and 200 mg/200 grams of mice, so that the dose was modified in this study to 750 mg/KgBW, 875 mg/KgBW, and 1000 mg/KgBW which were given orally. [12] While the administration of CCl_4 in previous studies found damage to rat hepatocytes induced by CCl_4 at a dose of 1.3 ml/kgBW of mice injected intraperitoneally and became the author's basis for administering treatment to mice in this study. [13]

Data analysis: Data were analyzed using the *Statistical Product and Service Solution* (SPSS) 17 program, to conduct a normality test using *Shapiro-Wilk* and obtained a normal data distribution (p value> 0.05). Continued with the *One Way Anova test* , a significant meaning was found (p value <0.05) and the data was continued with a Post Hoc analysis test to find a comparison of each group.

RESULTS AND DISCUSSION

The study was conducted experimentally in a laboratory to assess the hepatoprotective effect of ethanol extract of clove flowers (EEBC) on 25 hepatocyte samples of rats with carbon tetrachloride induction, which were divided into 5 groups, each containing 5 rats, namely:

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1. Group 1 (K1): Negative control, without any treatment, only given diet and drink.
2. Group 2 (K2): Positive control, same as K1, but induced by CCl_4 in the second stage of treatment.
3. Group 3 (K3): given EEBC of 750 mg/KgBW.
4. Group 4 (K4): given EEBC of 875 mg/KgBW.
5. Group 5 (K5): given EEBC of 1000 mg/KgBW.

One rat from each group did not survive and entered the *drop out category* . The treatment started from the first stage from day 1 to day 7, where K1 and K2 were not given any treatment, while K3 was given EEBC of 750 mg/KgBB, K4 was given EEBC of 875 mg/KgBB and K5 was given EEBC of 1000 mg/KgBB, which was given in a single dose per day. On day 8, all rats other than K1 were induced with CCl_4 intraperitoneally as much as 1.3 ml/KgBW.

Qualitative Observation of Results

Rat hepatocytes were made into preparations with *Haemotoxylin Eosin* (HE) staining, then assessed quantitatively based on the impression of damage to rat hepatocytes and differences were found in each treatment group. In the negative control group (K1), which was not given any treatment other than diet and drink during the first and second stages, hepatocytes were seen with a polyhedral shape, clear boundaries with a monomorphic nucleus and cytoplasm full of mitochondria, which resembled a normal liver lobule shape. [14,15] The image of hepatocytes in the K1 experimental group can be seen in Figure 1.

Meanwhile, in the positive control group (K2) which was given diet and drink, and induced with CCl_4 as much as 1.3 ml/KgBW intraperitoneally on the 8th day, there was cell damage in the form of necrosis and some degeneration at 400x magnification, which can be seen in Figure 2. Hepatocytes that experienced necrosis did not have a clear cell shape compared to hepatocytes in general, the hepatocyte nucleus was irregular with almost invisible cytoplasm. In cells that experienced degeneration, it was seen that they did not have an intact shape, the nucleus was mostly polymorphic, for parenchymal degeneration the cytoplasm widened and was cloudy, and for hydropic degeneration the widened cytoplasm was colorless. This degeneration is caused because the cell membrane formed by polyunsaturated fats is damaged due to the active substance CCl_4, trichloromethyl, which when reacted with oxygen forms trichloromethyl peroxide (CCl_3O_2) which can attack the endoplasmic reticulum lipids of the cell membrane so that it will disrupt Ca^{2+} homeostasis and ultimately result in leakage of extracellular fluid into the cytoplasm, disruption of the hepatocyte structure, and so on.
necrosis. [16,17]

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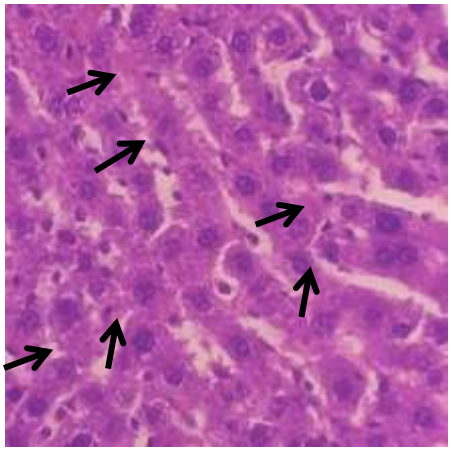

Figure 1 Hepatocyte Network K1 in HE 400x Staining Hepatocytes have clear boundaries with regular sinusoids; Normal Cells (black arrows).

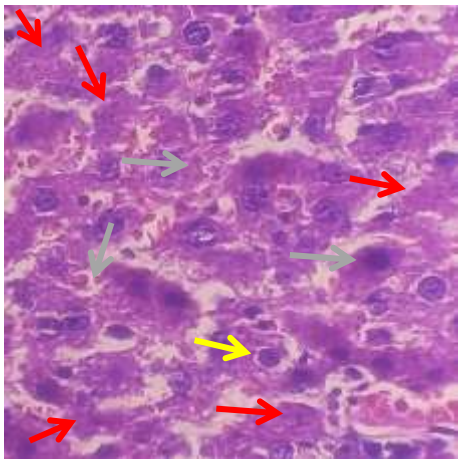

Figure 2 K2 Hepatocyte Network in HE 400x Staining Hepatocyte boundaries are not clearly visible and sinusoids are irregular. Parenchymal degeneration (green arrows), hydropic degeneration (yellow arrows), and cell necrosis (red arrows).

Group 3 (K3) treated with EEBC dose of 750 mg/KgBW/day in the first stage and induced with CCl_4 As much as 1.3 mg/KgBW in the second stage, obtained a picture at 400x magnification, some hepatocytes experienced necrosis damage and cell degeneration. Hepatocytes still appear to be dominated by degeneration and necrosis, but the number of normal cells appears to be greater than K2, as can be seen in Figure 3.

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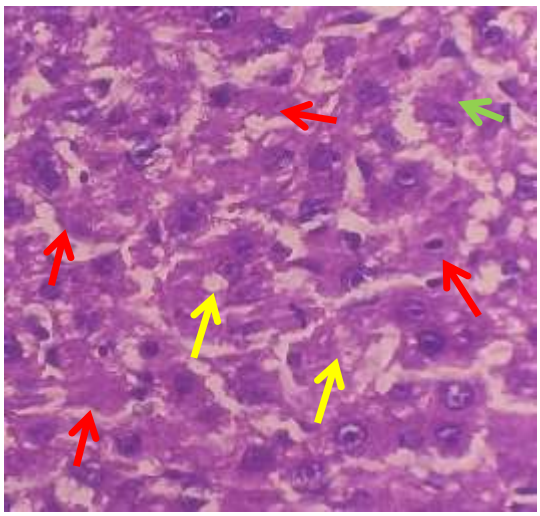

Figure 3 K3 Hepatocyte Network on HE 400x Staining Parenchymal degeneration (green arrows), hydropic degeneration (yellow arrows), and cell necrosis (red arrow)

Group 4 (K4) which was treated the same as K3, only differing in the dose of EEBC given, which was 875 mg/KgBW/day, obtained an image at 400x magnification, normal hepatocytes began to appear and damage was reduced to a lighter degree, but some cells that experienced degeneration and necrosis could still be found. K4 found more normal hepatocytes compared to K3, which can be seen more clearly in Figure 4.

In group 5 (K5) which received the same treatment as K3 and K4, only differing in the dose of EEBC, which was 1000 mg/KgBW/day, the microscopic image with 400x magnification showed more normal hepatocytes compared to K4 with fewer degenerating and necrotic cells. Normal hepatocytes were seen to have clearer hepatocyte and sinusoid boundaries. The image can be seen more clearly in Figure 5.

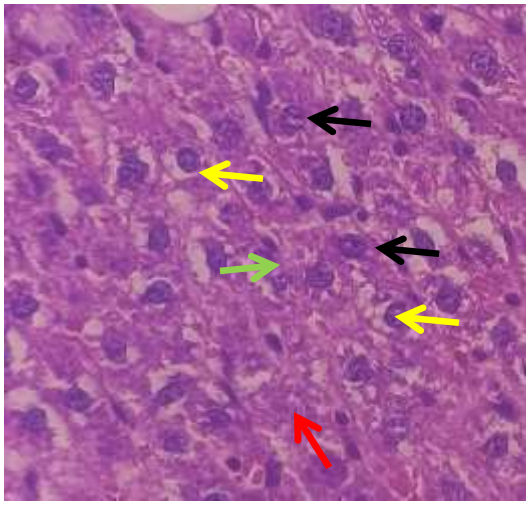

Figure 4 Hepatocyte K4 tissue on HE 400x staining Normal cells (black arrows), parenchymal degeneration (green arrows), hydropic degeneration (yellow arrow), and cell necrosis (red arrow)

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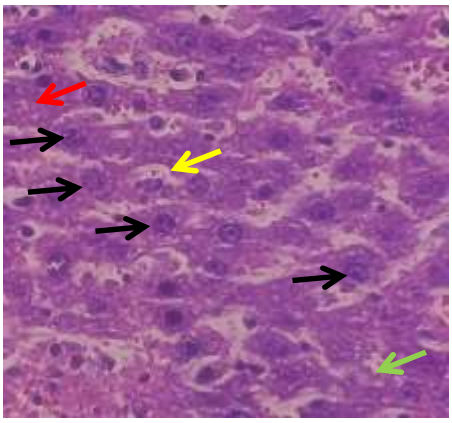

Figure 5 K5 Hepatocyte Network in HE 400x Staining Normal cells (black arrows), parenchymal degeneration (green arrows), hydropic degeneration (yellow arrow), and cell necrosis (red arrow)

Quantitative Observation of Results

Manja *Roenigk* scoring , by counting cells with 400x magnification from five fields of view, then summed and averaged. The average obtained has a range between 1 and 4. A value approaching 1 means that normal hepatocytes are more dominant, while a value approaching 4 means that more hepatocytes experience cell necrosis. Scores with low averages are K1 and K5. While K3 has a higher average than the positive control, it is suspected because there is 1 sample from K3 whose average is abnormal, so it becomes a confounder. Researchers suspect this is due to individual mouse factors that researchers cannot overcome. The results of the *Manja Roenigk scoring calculation* in more detail can be seen in Table 1.

The data obtained were then processed statistically using the *Shapiro Wilk test* because the sample size was ≤50, a p value of >0.05 was obtained which means a normal distribution and continued with the *One-Way ANOVA test* and a p value of <0.05 was obtained which means there was a significant difference between all groups so that it can be continued with the *Post Hoc test* to determine the meaning of the differences in each treatment group. The results of the *Post Hoc test* can be seen in Table 2.

Table 1 Score calculation results

No.	Group	Number of Samples (n)	Average
1	K1	4	1.12
2	K2	4	1.92
3	K3	4	2.04
4	K4	4	1.90
5	K5	4	1.48

Information:
K1: Negative control

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K2: Positive control
K3: given EEBC of 750 mg/KgBW
K4: given EEBC of 875 mg/KgBW
K5: given EEBC of 1000 mg/KgBW

Table 2 Results of the *Post Hoc test* of the treatment group with interpretation

No.	Comparison	Group	Value p* Group	Interpretation
1	K1	K2	0.000	Significantly different
		K3	0.000	Significantly different
		K4	0.000	Significantly different
		K5	0.036	Significantly different
2	K2	K3	1.000	Not Significantly different
3	K4		1.000	Not Significantly different
4	K5		0.004	Significantly different
5	K3	K4	1.000	Not Significantly different
6	K5		0.001	Significantly different
7	K4	K5	0.011	Significantly different

Post Hoc test results p≤0.05 indicate a significant difference. Note:
K1: Negative control
K2: Positive control
K3: given EEBC of 750 mg/KgBW
K4: given EEBC of 875 mg/KgBW
K5: given EEBC of 1000 mg/KgBW

Post Hoc Test results showed significant differences between K1 and K2, K3, K4, and K5. K1 and K2 are negative and positive controls and there are differences between the two. This is because K1 is dominated by normal cells and K2 is dominated by damaged cells. This could underlie the fact that CCl3 $_{has}$ worked to damage rat hepatocytes. Samples K3, K4, and K5 are different from K1, indicating that there are no samples that resemble the negative control group. K5 showed significant differences with K2, indicating that K5 is not similar to the positive control group.

Post Hoc test shows that CCl_4 is toxic to hepatocytes qualitatively or quantitatively, as seen from the results of K1 and K2, proving that CCl_4 damages cells through lipid peroxidation indicated by the presence of degenerated cells. CCl_4 in the liver will be metabolized by the cytochrome P-450 enzyme, converted into a free radical reactive metabolite CCl_3, which reacts with oxygen to form a compound trichloromethyl peroxide (CCl_3O_2) which can attack the endoplasmic reticulum lipid of the cell membrane, thereby disrupting Ca^{2+} homeostasis and ultimately causing cell death. [16,17]

K3, K4 and K5 statistically have significant differences with the negative control group (K1), which means that there is no treatment group that is similar to the number of normal

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cells in K1. Although K5 is significantly different from K1, K5 is not similar to K2 indicating that in K5 there is a hepatoprotective effect, but it is still not close to normal cells. This supports previous research on the use of a dose of 1000 mg/KgBB. [11]

Previous studies using EEBC in mice with doses of 100 mg, 200 mg, and 400 mg found an increase in the locomotor activity of mice, also explaining the content of EEBC in the form of eugenol and flavonoids. [12] Researchers found that both substances had an effect as hepatoprotectors and proved a greater effect with higher doses and concentrations. In another study using EEBC at a dose of 1000 mg/KgBW, a statistically significant hepatoprotective effect was also found, but using paracetamol as an inducer. [11] While this study used CCl_4 which had a stronger effect and a faster half-life, causing greater damage and is thought to be a factor that also influences the effectiveness of EEBC in preventing hepatocyte damage as proven in this study. This is thought to be the reason K3 and K4 did not find a statistically significant difference to the positive control.

The difference between paracetamol induction and CCl_4 is that paracetamol will cause accumulation of *N-acetyl-pbenzoquinoneimine* (NAPQI) in the liver, is reactive and can damage hepatocytes by covalent bonds formed in liver proteins causing damage to cell membranes and mitochondrial dysfunction. While CCl_4 is a free radical that does not require a large amount, but can cause greater damage. Even so, this study proves the hepatoprotective effect of EEBC at a dose of 1000 mg/KgBW qualitatively and statistically significant. [11,18]

Clove flowers contain antioxidants including flavonoids, eugenol, phenol, tannin, and saponin, which have hepatoprotective activity. [19,20] The eugenol content in cloves has the effect of inhibiting the process of lipid peroxidation, LDL and VLDL oxidation. [21] Meanwhile, flavonoids have the greatest antioxidant effect because they have phenolic hydroxyl groups that have the power to capture free radicals. [21] Both function to reduce free radicals because the OH group replaces glutathione (GSH), changes reactive metabolites from free radicals into non-active metabolites, is hydrophilic so that it is easily excreted. In addition, flavonoids function as vasodilators that accelerate the reduction of free radicals in blood vessels. [21]

CONCLUSION

Based on the results of the study of the hepatoprotective effect of ethanol extract of clove flowers induced by CCl_4, it can be concluded that ethanol extract of clove flowers (EEBC) provides a hepatoprotective effect at a dose of 1000 mg/KgBW on rats induced by CCl_4, and this dose also provides the best hepatoprotective effect on hepatocytes of *Wistar strain rats* in the study. Based on the research that has been conducted, it is recommended to conduct further research on EEBC with a dose level of more than 1000 mg/KgBW to find the most effective dose on CCl4-induced hepatocytes , further research on how to process clove husks to produce better effectiveness, and in-depth phytochemical research to determine the content of EEBC.

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