International Journal of Engineering Inventions
e-ISSN: 2278-7461, p-ISSN: 2319-6491
Volume 12, Issue 4 [April. 2023] PP: 110-115

Activity Test Of Turmeric Ethanol Extract (Curcuma Longa Linn.) As Cardioprotector in Doxorubicin-Induced Wistar Rats

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ABSTRACT: *The use of chemotherapy drugs causes most cardiotoxicity events. The main compounds of turmeric are curcuminoids, which give turmeric its yellow color. Curcuminoids are the center of attention for researchers to study their safety, antioxidant properties, anti-inflammatory, anti-cancer properties, and ability to reduce heart attack risk. The purpose of testing the effectiveness of turmeric ethanol extract (EEK) on experimental animals induced by doxorubicin on the heart organ with the parameters measured are CK-MB (Creatine kinase-MB) and LDH (Lactate dehydrogenase). This type of study was experimentally conducted in August 2022, as well as the execution of rats and the delivery of blood and organ samples at the end of October 2022. This research was conducted at the Pharmacology Laboratory of the Faculty of Pharmacy, University of North Sumatra. Turmeric ethanol extract can reduce the levels of biomarkers of heart damage, namely CK-MB and LDH. They were induced with doxorubicin. Giving a dose of turmeric ethanol extract gradually increases can reduce the incidence of heart cell damage, where the most effective at a dose of EEK 500 mg / kgBB. Furthermore, Turmeric ethanol extract has cardioprotective effects induced by doxorubicin.*
Keywords: *doxorubicin, turmeric, cardioprotective*

Date of Submission: 01-04-2023 Date of acceptance: 12-04-2023

I. INTRODUCTION

Doxorubicin (DOX), one of the most common chemotherapeutic agents for various cancer therapies, comes from the anthracyclines class of antibiotics. The side effects of doxorubicin are irreversible in chronic use, including the formation of cardiomyopathy, congestive heart failure, nephrotoxic, and hepatotoxic. The risk of using doxorubicin causes side effects on normal tissues, especially in the heart, and causes immune system suppression. Cardiotoxicity is when damage to the heart and blood vessels occurs due to toxic chemical exposure. The use of chemotherapy drugs causes most cardiotoxicity events. The high number of cardiotoxicity cases due to the use of anthracyclines chemotherapy drugs, with an incidence rate reaching 86.8%. One of the anthracyclines drugs often used is doxorubicin which can cause cardiotoxicity. In a study conducted by Eisvand et al. (2022), the administration of doxorubicin 4 mg/kg BW in mice, which was carried out once a week for four weeks intraperitoneally (IP), there was an increase in cardiac fibrosis when compared to the control group that was not given doxorubicin (1). Because of the effects caused by doxorubicin, an active compound that can protect the heart organ (cardioprotective) is needed; this cardioprotective compound can provide good anti-inflammatory and antioxidant effects. Turmeric, with the scientific name Curcuma longa Linn, is one of the spice plants and is also a medicinal plant. The main compounds of turmeric are curcuminoids, which give turmeric its yellow color. These curcuminoids are the center of attention for researchers to study their safety, antioxidant properties, anti-inflammatory, anti-cancer properties, and ability to reduce heart attack risk. In studies conducted in vitro, curcumin compounds contained in turmeric rhizomes are cytotoxic, inhibiting the proliferation of cancer cells and reducing the pain or size of cancer wounds. Therefore, turmeric is likely to be used as an anti-inflammatory and very useful for anti-cancer therapy. Thus the potential of turmeric as a medicinal plant can be studied more deeply so that its use as a traditional medicine can be maximized again without adverse side effects (2).

Vitamin E is an antioxidant that has been popular in the health world, known to be effective in scavenging free radicals generated by radiation exposure as a powerful breaker of the leading lipid chains found in the body (1). As an antioxidant, vitamin E maintains the stability and integrity of cell membranes and protects cells from the toxicity of various drugs, heavy metals, and other chemical compounds that form free radicals. Based on the description above, long-term cancer therapy with doxorubicin often causes multiorgan damage, one of which can cause cardiotoxicity. The turmeric plant (Curcuma longa linn = Tumeric), with a rich content of curcuminoids (curcumin), has properties as a potent free radical scavenger, thus encouraging researchers to test the effectiveness of turmeric ethanol extract (EEK) on experimental animals induced by doxorubicin on the heart organ with the parameters measured are CK-MB (Creatine kinase-MB) and LDH (Lactate dehydrogenase) as biomarkers and conduct a histopathological examination of heart tissue in experimental animals.

II. LITERATURE REVIEW

Doxorubicin is an antibiotic of the anthracycline group that is widely used for the therapy of various types of cancer and is one of the most influential and essential antineoplastic agents in clinical use (3). However, its clinical use has been restricted mainly due to the potential for organ toxicity, which can cause cardiotoxicity. Cardiotoxicity is damage that occurs to the electrophysiology of the heart or damage to the heart muscle. In this condition, the heart becomes weak and inefficient in pumping blood throughout the body. This condition can also occur due to chemotherapy treatment. Although the effects of cardiotoxicity can be acute or chronic, in critical events, this cardiotoxic effect occurs quickly and generally occurs during chemotherapy administration or in the first year of chemotherapy administration; in this situation can be found in the form of arrhythmias, myocardial ischemia, vasospastic and thromboembolism, pericarditis or myocarditis-like syndrome. Whereas in the chronic state, cardiotoxic effects occur slowly, at least one year after chemotherapy is completed, usually including left ventricular dysfunction (LVD) with or without congestive heart failure (CHF), arterial hypertension (HTN), and QTc prolongation. In using anthracycline antibiotics for chemotherapy, acute cardiotoxic effects are less than chronic cardiotoxic effects (4).

The occurrence of cardiotoxicity by doxorubicin is caused by the formation of ROS (reactive oxygen species), a process of iron metabolism with increased oxidative stress in the myocardium. Oxidative stress mechanisms most often cause heart damage due to using anthracycline-class antibiotics (5). Various sources mention that turmeric (Curcuma longa Linn) or its main compound, curcumin, can be used as a therapy for diseases related to the cardiovascular system. Curcumin can be known to be closely related to the cardiovascular system through pharmacological activity (6).

III. RESEARCH METHODS

This type of study was experimentally conducted in Agustus 2022, as well as the execution of rats and the delivery of blood and organ samples at the end of Oktober 2022. This research was conducted at the Pharmacology Laboratory of the Faculty of Pharmacy, University of North Sumatra.

Tools, materials and experimental animals

The tools used in this study were veterinary surgical tools, laboratory glassware, microscopes, 1 ml syringe, 3 ml syringe, oral sonde, centrifuge, test tubes, animal balances / analytical balances, beaker glass, mortar, stamfer, spatula, parchment paper, measuring flask, cuvettes, microtubes, micropipettes, rotarymikrotoms, water baths, and object glasses. The ingredients used in this study were EEK (Turmeric Ethanol Extract) derived from fresh turmeric purchased at Sei Sikambing Medan Market, Doxorubicin, NaCl, 10% formalin, chloroform, CMC-Na, liquid paraffin, toluene, and acetone, CK-MB and LDH reagents. The animal used in this study was a male Wistar rat (Rattus norvegicus) with a weight of 150 – 200 grams. Before this study was conducted, the test animals would be acclimatized for one week under room temperature conditions (22-25°C), under a light/dark 12-hour cycle, and given pellets and tap drinking water ad libitum. Before conducting research, researchers will seek Ethical clearance approval from the research ethics committee for research involving living things so that this research is feasible, and the results of the experiment can be published in national and international journals.

Preparation of Turmeric Ethanol Extract Test Ingredients

In this study, the sample used was the rhizome of yellow turmeric (Curcuma longa Linn). This phytochemical screening was carried out to determine the group of compounds from alkaloids, flavonoids, glycosides, saponins, tannins, and steroids/triterpenoids (Ministry of Health RI, 1995., Farnsworth, 1996), conducted at the Biology Laboratory of the Faculty of Pharmacy, University of North Sumatra.

Solution manufacturing includes the manufacture of a 0.5% w/v CMC-Na suspension and an EEK suspension at doses of 100, 300, and 500 mg/kg body weight. The cardioprotective effectiveness test procedure refers to several studies, namely; El-Sayed, et al 2011; Aggarwal, et al 2009; Greetings et al 2016. The in vivo test in the experiment used as many as 24 (twenty-four) mice divided into 6 (six) groups and each group consisted of 4 (four) mice, namely:

a. Group I (Normal): The group of male wistar rats (Rattus norvegicus) was only given feed and Na – CMC 0.5%.
b. Group II (Negative control): The group of male wistar rats (Rattus norvegicus) were given doxorubicin 5 mg/kg body weight on an i.p basis and drank a 0.5% Na-CMC suspension.
c. Group III (Positive control): The group of male wistar rats (Rattus norvegicus) induced doxorubicin 5 mg/kg body weight 1 day 1 time on day 1, 7, 14 and 20 on i.p+ Vitamin E 1 % BB orally 1 time 1 day daily.
d. Group IV: The group of male wistar rats (Rattus norvegicus) induced doxorubicin 5 mg/kg body weight 1 day 1 time on day 1, 7, 14 and 20 i.p + 100 mg/kg body weight EEK orally 1 time 1 day daily.
e. Group V: The group of male wistar rats (Rattus norvegicus) induced doxorubicin 5 mg/kg body weight 1

day 1 time on day 1, 7, 14 and 20 i.p + 300 mg/kg body weight EEK orally 1 time 1 day daily.

f. Group VI: Group of male wistar rats (Rattus norvegicus) induced doxorubicin 5 mg/kg body weight 1 day 1 time on day 1, 7, 14 and 20 i.p + 500 mg/kg body weight EEK orally 1 time 1 day daily.

Then on the 21st day the rats will be satisfied for 18 hours then all the experimental animals are anesthetized with chloroform and then sacrificed. Furthermore, blood was taken from the rat's heart to check the levels of CK-MB and LDH.

Analysis of CK-MB and LDH Levels

Examination of Creatine kinase-MB (CK-MB) levels with Reagent set from Pointe Scientific, Inc. , USA. The CK-MB reagent is for quantitative determination of creatine kinase-MB (CK-MB) isoenzymes in serum, and only for in vitro diagnostic use. LDH is an enzyme that almost all cells in the body have, including blood cells, muscles, brain, kidneys, pancreas, heart, and liver.

Table 1. Normal values of LDH (Ethics and Savitri. 2017).

No.	AGE	NORMAL VALUES	UNIT
1.	0 – 10 Days	290 – 2000	U / L
2.	10 Days– 12 Years	180 – 430	U / L
3.	2 Years – 12 Years	110 – 295	U / L
4.	More than 12 Years	100 – 190	U / L

Manufacture of Cardiac Tissue Preparations

Manufacture of cardiac tissue preparations by the procedure outlined by Miranda- Osorio., (2016). The organ is fixed with a 10% formalin solution for 3-4 hours, then with acetone 3 times (for 2 hours each). After that, cleaning is carried out using toluene 3 times (1-2 hours each). The embedding process of the sample in liquid paraffin at a temperature of 60-70 ° C was carried out 3 times (each for 2 hours), then the process of printing the paraffin block was carried out. The cutting stage of the paraffin block is carried out using micro toms so that a sheet with a thickness of 5 µm is obtained. The sheet is placed in a water bath whose temperature is 30 °C then attached to the object-glass and heated in the oven for 2-3 minutes. The resulting sheet is observed under a light microscope with a magnification of 10x40, an observed number of necrosis, and normal cells (Salam, 2016). Before blood and tissue samples are sent to the Integrated Clinical Laboratory Installation of the University of North Sumatra Teaching Hospital, the sample is first given a sample code, to make it easier for researchers to calculate statistically, among others :

Data Analysis

The data were analyzed using the Shapiro-wilk method to see the normality of the data. If the data is normally distributed ($P > 0.05$), proceed using the One Way ANOVA method to determine the average difference between the groups. If there is a difference, ($P < 0.05$) followed by the Post Hoc Tukey HSD test to see the real difference between treatments. But if the distributed data is abnormal then the Kruskal-Wallis test is used.

Results And Discussion

Based on sample identification results obtained from Turmeric Ethanol Extract comes from the Zingiberaceae family of the genus Curcuma species Curcuma longa or Curcuma domestica val.

Table 2. Phytochemical screening results of turmeric ethanol extracts

No	Screening	Results
1	Alkaloid	+
2	Flavonoid	+
3	Glycoside	+
4	Saponin	+
5	Tannin	+
6	Steroid/triterpenoid	+

Description ; (+) : Present ; (-) : Not available

Based on the results of the examination carried out, results were obtained in the normal group of serum CK–MB levels very much different from the negative group induced by doxorubicin, the I EEK treatment group

100 mg/kg body weight + doxorubicin accumulative dose 20 mg/kg body weight. Normal group CK – MB levels did not differ much from the treatment group III EEK 500 mg/kg body weight + doxorubicin accumulative dose 20mg/kg body weight, the positive control group doxorubicin accumulative dose 20 mg/kg body weight+ vitamin E 1% BB and treatment group II doxorubicin accumulative dose 20 mg/kg body weight + EEK 300 mg/kg body weight. In theory, the normal value for serum CK – MB levels in healthy humans ranges from 3–5% of the total Creatine–Kinase value which means CK–MB normally remains in circulation (Cabaniss, 1990).

Table 3. Serum Levels of CK – MB

Treatment Group	CK-MB ±SD (U/L)
Normal Group	311,24 ± 5,00
Negative Group (Doxorubicin Induction 20 mg/kgBB + Na-CMC 0.5%)	876,19 ± 7,67
Positive control group (Doxorubicin induction 20 mg/kgBB + Vitamin E 1% BW)	403,41 ± 3,19
Treatment Group I; Rats induced by Doxorubicin 20 mg/kgBB + EEK 100 mg/kgBB	678,12 ± 10,11
Treatment Group II; Rats induced by Doxorubicin 20 mg / kgBB + EEK 300 mg / kgBB	427,03 ± 2,46
Treatment Group III; Rats induced by Doxorubicin 20 mg / kgBB + EEK 500 mg / kgBB	365,24 ± 45,12

As seen in table 3, it is known that the results for the standard group serum CK-MB values were 322.44 ± 5.00 U/L. On the other hand, the opposing group induced only by doxorubicin had the highest serum CK-MB levels of 876.19 ± 7.67 U/L. This is due to the formation of free radicals from doxorubicin, which increases oxidative stress and is believed to be the forerunner of cardiotoxicity (Minotti et al., 1999). Meanwhile, treatment group I EEK 100 mg/kgBB + doxorubicin had the highest serum CK-MB level of 678.12 ± 10.11 U/L. And treatment group III EEK 500 mg/kgBB + doxorubicin had the smallest serum CK-MB level of 365.24 ± 45.12, close to the standard group. This shows that EEK 500 mg/kgBB can reduce doxorubicin-induced CK-MB levels.

Based on the statistical test results, serum CK-MB levels in the standard group had a significant difference ($p<0.05$) with the negative control treatment group and treatment group I. Still, they did not have a significant difference ($p>0.05$) with the positive control group, treatment groups II and III. On the other hand, the serum CK-MB levels of the negative control group had a significant difference ($p<0.05$) with the regular group, favorable control treatment, treatment group I, treatment group II, and treatment group III.

The serum CK-MB levels of the positive control group had a significant difference ($p<0.05$) with the negative control treatment group and treatment group I. They had no significant difference ($p>0.05$) with the standard control group, treatment group II, and treatment group III. Serum CK-MB levels in treatment group I had a significant difference ($p<0.05$) with the regular group, positive control group with vitamin e 1% BW, treatment group II, and treatment group III. Serum CK-MB levels in treatment group II had a significant difference ($p<0.05$) with the opposing group and treatment group I and had no significant difference ($p>0.05$) with the regular group, positive control group, and treatment group III.

Serum CK-MB levels in treatment group III had a significant difference ($p<0.05$) with the opposing group and treatment group I and had no significant difference ($p>0.05$) with the regular group, positive control group, and treatment group II. In this study, serum LDH levels were examined from the blood of male Wistar rats. The examination was carried out at the Integrated Clinical Laboratory Installation of the University of North Sumatra Teaching Hospital. Based on the study results obtained in the standard group, the value of serum LDH levels significantly differed from the opposing group induced by doxorubicin, treatment group I EEK 100 mg / kgBB + accumulative doxorubicin dose of 20 mg / kgBB. LDH levels in the standard group were not significantly different from the treatment group III EEK 500 mg/kgBB + doxorubicin accumulative dose of 20 mg/kgBB, positive control group doxorubicin accumulative dose of 20 mg/kgBB + vitamin E 1% BB and treatment group II doxorubicin accumulative dose of 20 mg/kgBB + EEK 300 mg/kgBB. The increase in LDH levels in the negative group could also be due to low levels of endogenous antioxidants in the heart, which makes the myocardium very sensitive to damage caused by free radicals from doxorubicin (Olson et al., 1990). The results of the examination can be seen in the table 4.

Table 4. Serum LDH Levels

Treatment Groups	LDH ± SD (U/L)
Normal Group	526,12 ± 5,21
Negative Group (Induction of Doxorubicin 30 mg/kg BW + Na-CMC 0.5%)	2665,20 ± 4,15
Positive Control Group (Doxorubicin Induction 30 mg/kg BW + Vitamin E 1% BW)	645,22 ± 3,12
Treatment Group I; Rats Induced Doxorubicin 30 mg/kg BW + EEK 100 mg/kg BW	1327,23 ± 81,23

Treatment Group II; Rats induced with Doxorubicin 30 mg/kg BW + EEK 300 mg/kg BW	847,46 ± 2,80
Treatment Group III; Rats induced with Doxorubicin 30 mg/kg BW + EEK 500 mg/kg BW	689,54 ± 3,18

Judging from the results of serum LDH research in the tables and figures on the previous page, it is known that the results for the standard group's serum LDH values are 526.12 ± 5.21 U/L. The opposing group induced only by doxorubicin had the highest serum LDH levels of 2665.20 ± 4.15. The increase in LDH levels due to oxidative stress that affects Ca^{2+} homeostasis occurs directly through the induction of mitochondrial permeability transition with changes in calcium transport in mitochondria. Because these changes eventually cause damage and even death to heart cells, followed by releasing several biomarkers into circulation (Schimmel et al., 2004).

While treatment group I EEK 100 mg/kgBB + doxorubicin had the highest serum LDH levels of 1327.23 ± 81.23 U/L. And treatment group III had minor LDH serum levels of 689.54 ± 3.18 U/L, close to the standard group. Like CK-MB serum levels, LDH serum levels showed that EEK 500 mg/kgBB could reduce doxorubicin-induced LDH levels. This indicates that the curcumin compound contained in turmeric rhizome can prevent free radical damage caused by doxorubicin starting from the smallest dose of 100 mg/kgBB.

Based on the statistical test results, LDH serum levels in the standard group had a significant difference ($p<0.05$) with the negative control treatment group and treatment group I. Still, they did not have a significant difference ($p>0.05$) with the positive control group, treatment groups II and III. The serum LDH level of the negative control group had a significant difference ($p<0.05$) with the regular group, favorable control treatment, treatment group I, treatment group II, and treatment group III. The serum LDH level of the positive control group had a significant difference ($p<0.05$) with the negative control treatment group and treatment group I and had no significant difference ($p>0.05$) with the standard control group, treatment group II and treatment group III.

LDH serum levels in treatment group I had a significant difference ($p<0.05$) with the regular group, positive control group with vitamin e 1% BW, treatment group II, and treatment group III. LDH serum levels in treatment group II differed significantly ($p<0.05$) from the opposing group and treatment group I. They had no significant difference ($p>0.05$) with the regular, positive control, and treatment groups III. LDH serum levels in treatment group III differed significantly ($p < 0.05$) from the opposing group and treatment group I. They had no significant difference ($p>0.05$) with the regular, positive control, and treatment groups II.

Thus, this study shows that turmeric ethanol extract reduces serum levels of CK-MB and LDH. Furthermore, the antioxidant ability of turmeric rhizomes is believed to neutralize free radical compounds, form enzymes that inhibit oxidative reactions such as cytochrome P-450, and stop the formation of chelating, which is the oxidation process of Fe metal ions so that no more oxidation reactions occur (Hartati, 2013). So it was concluded that EEK has cardioprotective effectiveness for the heart of male Wistar rats induced with doxorubicin.

Table 5. Histology levels of heart cells of male wistar rats

Treatment Groups	Bleeding	Cardiolysis	Piknosis	Fragmentation
Normal Group	-	-	-	-
Negative Group (Induction of Doxorubicin + Na-CMC 0.5%)	+++	+++	+++	+++
Positive control group (Induction of Doxorubicin + Vitamin E 1% BB)	-	-	-	+
Treatment Group I ; Rat Induced Doxorubicin + EEK 100 mg/kg body weight	++	++	++	++
Treatment Group II ; Rat Induced Doxorubicin + EEK 300 mg/kg body weight	-	+	+	++
Treatment Group III ; Rat Induced Doxorubicin + EEK 500 mg/kg body weight	-	-	-	+

Information:
(+++) : serious damage
(+) : minor damage
(++) : moderate damage
(-) : no damage occurred

Judging the table above shows that the normal group does not experience damage to the tissues of the heart organs where the myocytes appear normal and the boundaries between cells each other are visible and the

myofibril heart muscle fibers appear normal. In the III treatment group, there appeared to be no bleeding, charismatics, picnosis, and fragmentation that occurred only moderate damage. In contrast to the results of the examination in the negative group which was only induced by doxorubicin, it was clear that bleeding occurred, damage to some core cells, namely the occurrence of picnosis or cell damage characterized by shrinkage and the color tended to be darker, then continued to be karyolysis, namely the cells looked very pale and colorless, where this condition the cell nucleus has lost shape and then fragmentation and damage to the heart muscle. In the positive control group, it can be seen that cells only experienced mild fragmentation due to the administration of vitamin E which reduced the occurrence of cell damage. Treatment group, I showed administration of turmeric ethanol extract at a dose of 100 mg/kg body weight in doxorubicin-induced rats showing cells were moderately damaged.

Treatment group II showed that turmeric ethanol extract at a dose of 300 mg/kg body weight + doxorubicin cells still experienced moderate damage fragmentation, but cariolysis and picnosis suffered minor damage. In the III treatment group, a dose of 500 mg/kg body weight + doxorubicin showed that the cells recovered and only mild fragmentation occurred. It can be seen that administering turmeric ethanol extract can prevent the occurrence of doxorubicin-induced heart cell damage in rats, by increasing the dose of administration there is a decrease in damage to heart cells.

In this study, the cardioprotective ability of turmeric against cardiotoxicity induced by doxorubicin against rats was identified. The yellow crystalline compound found in turmeric, namely Curcumin, has traditionally been used medically because it is considered to have cardioprotective or chemopreventive effects against various cancers (7). The mechanism of occurrence of cardiotoxicity caused by the administration of doxorubicin is known from this study. The decrease in the level of the enzymes CK–MB and LDH due to the administration of doxorubicin confirms that the administration of Curcuma longa Linn has a cardioprotective effect derived from curcumin compounds. Turmeric ethanol extract prevents the occurrence of doxorubicin-induced histological changes in rat heart organ tissues, where turmeric ethanol extract can restore endogenous antioxidant activity or as an antioxidant / both (8). In line with research that has been carried out by El Sayed et al (2011), it was concluded that the administration of Curcuma longa Linn extract can reduce levels of CK–MB and LDH enzymes induced by doxorubicin.

From various current research data, it can be concluded that the administration of turmeric extract with doxorubicin can provide a cardioprotective effect on acute toxicity in the heart organs through the improvement of heart enzymes, modulating pathways that trigger cardiac apoptosis such as decreased GSH levels, increased calcium and excessive free radical production (9) and finally normalize antioxidant enzymes. Therefore, this study is expected to be able to recommend supplements based on turmeric so that they can be used in the treatment in combination with doxorubicin to protect against damage to the heart without reducing the expected clinical effects of doxorubicin, also expected to improve the quality of life of patients (7).

IV. CONCLUSION

Based on the results of research, observations and discussion, it can be concluded that:

1. Turmeric ethanol extract has the ability to reduce the levels of biomarkers of heart damage, namely CK-MB and LDH. induced with doxorubicin.
2. Giving a dose of turmeric ethanol extract gradually increases can reduce the incidence of heart cell damage, where the most effective at a dose of EEK 500 mg / kgBB.
3. Turmeric ethanol extract has a cardioprotective effect induced with doxorubicin.

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