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Electrocardiographically study of protective effect of *Eruca Sativa M.* versus doxorubicin induced cardiotoxicity in rabbits

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Abstract--Cardiotoxicity is defined as drug-induced damage to the heart muscle, which can result in cardiac failure or cardiac arrest. Cardiotoxicity is a common side effect of traditional anticancer drugs such as doxorubicin, taxanes, 5-fluorouracil, and cyclophosphamide, as well as newer agents such as biological antibodies such as Nivo. Cardiotoxicity is also caused by the long-term use of neurologic/psychiatric medications. This study was designed to determine the effect of *eruca sativa* mill (Gergeer) leaves extract on cardiotoxicity induced by doxorubicin in rabbits. The thirty-five rabbits used in this study were obtained from a local rabbit breeder. Animals ranged between 1-1.3 years old, and their weight was approximately 1-2kg without specifying gender. experiment: Thirty-five adult rabbits (n=35) will be randomly divided into four groups (7 rabbits/each group) first group: seven rabbits will receive distal water (D.W) orally (-ve control), Second group: fourteen rabbits divided into two subgroup equally administrated with doxorubicin 4 mg/kg B.W (I.P) between day to day for 14 days to induce cardiotoxicity (the first subgroup leave two weeks then killed, while the second subgroup leaves to 28 days without treatment), Third group: seven rabbits administrated with *Eruca sativa* mill Leaves ethanolic extract daily for 28 days Orally by stainless gavage needle, Fourth group: seven rabbits administrated with *Eruca sativa* Leaves ethanolic extract orally daily for 14 days as protective then we give doxorubicin 4 mg/kg B.W (I.P) between day to day for 14 days, While continuing to give *Eruca sativa* mill orally for 28 days. ECG Information about heart rate and monitoring of any irregularity in its rhythm. ECG Results in R-R duration show an significant decrease in all group as compared to control group, T amplitude show increase

significant in G4 and G3 compared with G2 and G1, T duration show decrease significant in G4 compared in the same group and other groups, QRS duration shows no sign in all group, QRS Amplitude show increase significant in G2 compared with G1, G3, and G4, S-T duration decrease significant in G2 compared with G1, G3, and G4, Q-T duration decrease significant in G2 compared with G1, G3, and G4. conclusion, The effective dose-response results asymptotic to 10 % of LD50, induced cardiac toxicity with DOX appear biochemically, cardiographically and histopathologically, The *Eruca sativa* mill (gergeer) extract was effective protective for induced cardiac toxicity.

Keywords---*eruca sativa* M, doxorubicin, ECG, cardiotoxicity, rabbit, Iraq.

Introduction

Cardio toxicity refers to the occurrence of myocardial injury and/or cardiac electrophysiological malfunction. Increased production of free radicals causes oxidative stress, which has been implicated in the pathophysiology of cardiovascular disorders such as ischemic heart disease, myocardial infarction, arrhythmias, atherosclerosis, and congestive heart failure (CHF) (Taleb et al., 2018). Cardio toxicity is a side effect of doxorubicin (DOX) that causes myocardial or valve damage. It can happen during or soon after treatment, days or weeks later, It may not become obvious for months, if not years, after cancer therapy has ended. Fatigue, anemia, and shortness of breath were signs of this consequence, indicating that the heart was having trouble performing its important activities (Kancharlapalli et al., 2014) .

Doxorubicin (DOX) is an antineoplastic drug that belongs to the anthracycline family. It has been the mainstay of cancer chemotherapy for decades, with well-established, highly effective, and notable successes in the treatment of both solid and hematological malignancies in both adult and pediatric patients (Shaker et al., 2018). Doxorubicin's principal method of action was the drug's ability to intercalate between DNA base pairs, inducing DNA strand breaking and inhibiting DNA and RNA synthesis. Also Doxorubicin inhibits topoisomerase II, resulting in DNA damage and death in cells. Furthermore Doxorubicin produced free radical-mediated oxidative damage to DNA when coupled with iron, significantly reducing DNA synthesis (Johnson-Arbor & Dubey, 2017). Doxorubicin cardiotoxicity mechanisms Reactive oxygen species (ROS), which are detrimental to cells, are created by oxidative stress in the mitochondria. Myocardial contractility disturbances are brought on by decreased Ca^{2+} uptake into the sarcoplasmic reticulum (SR), increased intracellular concentration of DOX brought on by changes in MDR efflux proteins, and decreased mesenchymal and circulating progenitor cells reduce the heart's capacity to regenerate after injury. (ROCKLEY, 2018) .

ECG exposure to the cardiac hazardous medication generates arrhythmia by prolonging cardiac repolarization (QT interval) (Torsades de pointes) (Iqbal et al., 2018). *Eruca sativa* Mill, often known as arugula, gergeer, or rocket leaves, is a

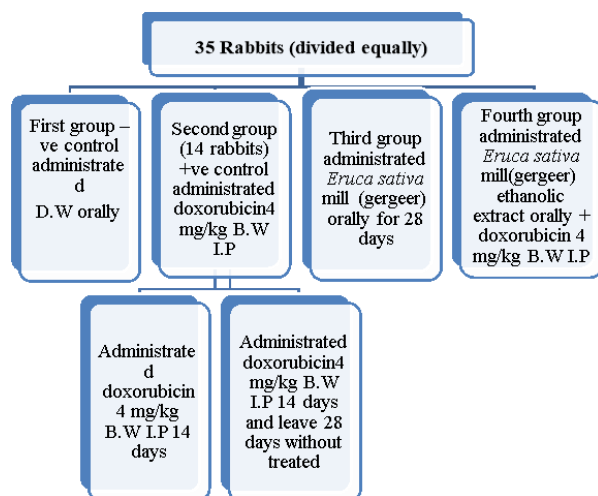
prominent plant of the Brassicaceae family (Turhan et al., 2022). It's also commonly used in salad dressings. The presence of various key elements, such as dietary fiber, oligosaccharides, amino acids, peptides, proteins, polyunsaturated fatty acids, vitamins, carbohydrates, L-ascorbic acid, and mineral content, makes *E. sativa* leaves a good source of nutrition.

Additionally, dieticians have noted that *E. sativa* is recognized for its low calorific content as well as strong nutritional benefits (Akgül et al., 2022). *E. sativa* has risen to prominence in recent years as a result of its high phytochemical content and importance in a variety of biological activities. Flavonoids, glucosinolates, phenolics, saponins, tannins, and essential oils are all found in different regions of the *E. sativa* plant (Ceccanti et al., 2018). Isothiocyanates, derivatives of butane, octane, nonane, 4-methylthiobutyl, isothiocyanate, cis-3-hexen-1-ol, 5-methylthiopentylisothiocyanate, cis-3-hexenyl 2-methylbutanoate, 5-methylthiopentane nitrile, quercetin, kampferol, rutin, The essential oil composition of the *E. sativa* seed was studied, and it was shown to have a considerable amount of sulfur and nitrogen compounds. Biological effects, such as antibacterial and antioxidant, are mainly attributed to active molecules created by essential oils and other phytoconstituents during secondary vegetal metabolism. Antimicrobial, antigenotoxic, antidiuretic, stimulant, stomach disorders analgesic, antioxidant, antiulcer, hepatoprotective activities, antidiabetic, antiacne, antihyperlipidemic, antihyperglycemic, and anti-inflammatory properties have been reported for a variety of phytochemicals found in *E. sativa*. In Central Asia, *E. sativa* seed oil, also known as taramira oil or jamba oil, is used for massages, hair treatments, and as an anti-influenza drug (Awadelkareem et al., 2022) .. investigation found that *E. sativa* had no discernible impact on VLDL levels (Salih, 2018; Weli et al., 2021).

Materials and Methods

Experiment

Thirty-five adult rabbits (n=35) will randomly divided into four group (7 rabbits/each group) as following: (A) first group: seven rabbits will received distal water (D.W) orally (-ve control), (B) Second group: fourteen rabbits divided to two subgroup equally administrated with doxorubicin 4 mg/kg B.W (Al-okaily et al., 2013) (+ve control) intraperitoneally (I.P) between day to day for 14 days to induce cardio toxicity (Swamy et al., 2011) (first subgroup leave two weeks then killed, while second subgroup leave to 28 days without treatment), (C) Third group: seven rabbits administrated with *Eruca sativa* mill (gergeer) Leaves ethanolic extract daily for 28 days Orally by stainless gavage needle, (D) Fourth group: seven rabbits administrated with *Eruca sativa* (gergeer) Leaves ethanolic extract orally daily for 14 days as protective then we give doxorubicine 4 mg/kg B.W (Al-okaily et al., 2013) intraperitoneally (I.P) between day to day for 14 days (Swamy et al., 2011). While continuing to give *Eruca sativa* mill (Gergeer) orally for 28 days.



Parameter Electrocardiography (ECG)

The Electrocardiography passes on data with respect to the electrical capacity of the heart, by adjusting the state of its constituent waves to be specific the P, QRS and T waves which is exact estimation of clinically essential parameters measured for the transient conveyance of the ECG constituent waves (Maglaveras et al., 1998). The measurement was obtained after two weeks and after four weeks. Recorded of the ECGs were by direct written work electrocardiogram (Belizna et al., 2007), all ECGs were institutionalized at 1mV = 10 mm, with a diagram velocity of 50 mm/sec., each box (small square) is 1 mm², figure (1-1) showed the normal features of the electrocardiogram durations and amplitudes with location of different waves (P, Q, R, S and T)

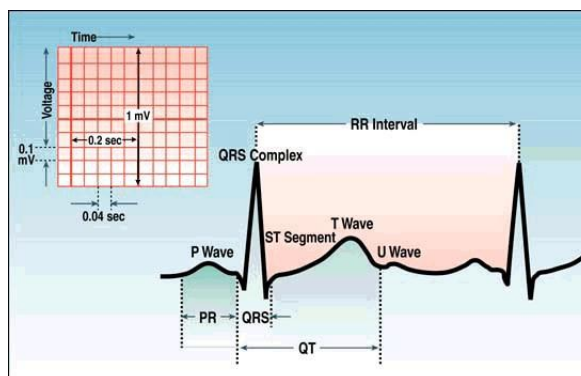


Figure 1-1. On the ECG paper, the graphic depicts normal ECG waves and periods, as well as typical time and voltage parameters (Kumar, 2007)

Normally, more than two electrodes are utilized, and they can be joined into various sets bipolar limb (I, II and III) leads and unipolar (aVR, aVL and aVF) Leads. Each lead looks at the heart from a different angle, (Lynch, 2014; Klabunde, 2013). Electrocardiography was evaluated by lead II which is limb lead. Leads of limb which are I, II and III. The signals that form by electrodes are situated one on the left leg and on the limbs one on each arm (Baxter *et al.*, 2014). Limb leads poses purposes of Einthoven's triangle (Lippincott Williams and Wilkins, 2009). Rabbit's hair was shaved for electrodes placement. Leads of limb, electrodes were placed on each leg after placed the rabbits in dorsal position (Rezakhani & Rezaian, 1995) on a table and then immobilized by ligation the four limb by bandage and they were left for 10-20 minutes to get calm. ECG were recorded. Modified wood table was used to record ECG waves (Figure 1-2).



Figure 1-2. Modified table for ECG recorded with bandage.

Results and Discussion

ECG Results

The R-R duration results in all group has a significant decrease ($P \leq 0.05$) as compared with control group within the group there is significant decrease in 4 weeks as compared to 2 week in G1, and significant decrease in 2 weeks as compared to zero and 4 weeks in G2 and there is significant decrease in 2 and 4 weeks as compared to zero time in G3 and G4 in 2 weeks and there is significant decrease in G3 and G4 as compared to G2 in weeks.

Table 1-1

The R-R Duration (ms) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	232 $\pm$ 7.61 A ab	238 $\pm$ 8.04 A a	222 $\pm$ 7.42 B b	14.05 *
G2- doxorubicin	244 $\pm$ 9.55 A a	215.6 $\pm$ 6.59 B b	233 $\pm$ 7.91 B a	15.98 *
G3 Eruca sativa	244 $\pm$ 9.55 A a	216 $\pm$ 6.59 B b	216.8 $\pm$ 6.88 B b	14.37 *

G4 Eruca sativa + doxorubicin	244 ±9.55 A b	216 ±6.59 B c	216.4 ±7.02 A a	14.94 *
LSD value	13.09 NS	16.73 *	15.47 *	---
Means with different big letters in the same column and small letters in the same row are significantly different. * (P≤0.05).				

Cardiac arrhythmia is the most evident myocardial dysfunction that occurs in early toxicant responses (Peters *et al.*, 2000). It has been emphasized the significance of varied K sensitivity among various myocardial fiber types and the modulation of the electrophysiologic effects of K by Ca and Na. There have been descriptions of arrhythmias brought on by electrolyte disturbances as well as the impact some electrolyte disturbances have on already-present arrhythmias. The impact of electrolyte disturbances on digitalis and antiarrhythmic drug activity, as well as the practical elements of electrolyte treatment (Borys Surawicz, 2006). The T amplitude in G3 and G4 has to increase significantly (P≤0.05) as compared with the control group and G2 in 2 weeks. and there is significant increase (P≤0.05) between G3 and G4 as compared with control group in 4 weeks, furthermore within the groups there sig increase at (P≤0.05) in G3 in 2 and 4 weeks as compared to zero time, also there is significant increase in 2 and 4 weeks as compared to control in G4. The T duration in G3 *Eruca sativa* has to increase significantly (P≤0.05) as compared G4. While within the group in G4 has to decrease significantly (P≤0.05) in 4 weeks as compared with 2 weeks and zero time at the same group and in G3 there is significant decrease in 4 weeks as compared to 2 weeks and zero time.

Table 1-2
The T Amplitude (mm) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	1±0.05 A a	1±0.05 B a	1±0.05 C a	0.202 NS
G2- doxorubicin	1±0.05 A a	1±0.05 B a	1.2±0.08 BC a	0.294 NS
G3 Eruca sativa	1±0.05 A b	1.8±0.26 A a	1.7±0.16 A a	0.378 *
G4 Eruca sativa + doxorubicin	1±0.05 A b	1.8±0.26 A a	1.5±0.12 AB a	0.309 *
LSD value	0.250 NS	0.446 *	0.392 *	---
Means with different big letters in the same column and small letters in the same row are significantly different. * (P≤0.05).				

Table 1-3
The T Duration (ms) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	0.052 ±0.02 A a	0.052 ±0.02 A a	0.052 ±0.02 AB ab	0.017 NS

G2- doxorubicin	0.052 ±0.02 A a	0.052 ±0.02 A a	0.052 ±0.02 AB ab	0.017 NS
G3 <i>Eruca sativa</i>	0.052 ±0.02 A a	0.068 ±0.03 A	0.072 ±0.03 A a	0.0193 *
G4 <i>Eruca sativa</i> + doxorubicin	0.052 ±0.02 A a	0.068 ±0.03 A a	0.048 ±0.01 B b	±0.0192 *
LSD value	0.017 NS	0.0172 NS	0.020 *	---
Means with different big letters in the same column and small letters in the same row are significantly different. * (P≤0.05).				

Values of T amplitude millimeter (mm) & T Duration millisecond (ms) decreased not significantly which indicated a decrease in cardiac intracellular K⁺ value, after a long period of administration the depletion of intracellular potassium contributes to toxicity (Sur *et al.*, 2021), and there is severe hyperkalemia in extract groups due to inhibition of Na⁺-K⁺-ATPase pump resulting in cellular misunderstanding and electrical tampering between AS node and AV node (Watanabe *et al.*, 2020). The QRS Duration result after 2 weeks refers to no significant differences at P≤0.05 G2 doxorubicin as compared to G4 *Eruca sativa* +doxorubicin and the control group. as well as there is no significant differences at (P≤0.05) between G3 *Eruca sativa* as compared to G4 *Eruca sativa* +doxorubicin and the control group. After 4 weeks of treatment, there is no significant difference between all groups. The QRS Amplitude result after 2 and 4 weeks in G2 doxorubicin refers to a significant increase at (P≤0.05) as compared with G3, G4, and the control group. while within the group at G2 there is significant increase at P≤0.05 between 2 and 4 weeks as compared to zero time and there is significant increase at (P≤0.05) in 2 weeks as compared to 4 weeks.

Table 1-4

The QRS Amplitude (mm) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	5.1 ±0.16 A a	5.2 ±0.18 B a	5.2 ±0.10 B a	0.403 NS
G2- doxorubicin	5.1 ±0.16 A c	8.7 ±0.37 A a	6.3 ±0.18 A b	1.21 *
G3 <i>Eruca sativa</i>	5.1 ±0.16 A a	5.2 ±0.11 B a	5.3 ±0.13 B a	0.571 NS
G4 <i>Eruca sativa</i> + doxorubicin	5.1 ±0.16 A a	5.2 ±0.10 B a	5.2 ±0.08 B a	0.508 NS
LSD value	0.348 NS	1.072 *	0.894 *	---
Means with different big letters in the same column and small letters in the same row are significantly different. * (P≤0.05).				

Table 1-5
The QRS Duration (ms) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	0.02 ±0.006	0.02±0.006	0.02±0.006	0.010 NS
G2- doxorubicin	0.02±0.006	0.02±0.006	0.02±0.006	0.010 NS
G3 Eruca sativa	0.02±0.006	0.02±0.006	0.02±0.006	0.010 NS
G4 Eruca sativa + doxorubicin	0.02±0.006	0.02±0.006	0.02±0.006	0.010 NS
LSD value	0.011 NS	0.011 NS	0.011 NS	---
NS: Non-Significant.				

R refers to ventricle & although increased not significantly but refers to enlargement in the left ventricle (Bornstein *et al.*, 2021), Patients with heart failure (HF) experience QRS prolongation, which is linked to a higher cardiac death rate. Progressive increases in QRS duration are seen in animals with dilated cardiomyopathy. This demonstrates that even the presence of increased left ventricular mass with higher cardiovascular (CV) may generate a rise in QRS duration. This study is in agreement with (Wiegerinck *et al.*, 2006). The QRS voltages were modestly but considerably raised at the superacute stage of myocarditis, according to the current study, On days 1 and 2, we did not record electrocardiograms. At this point, the pathological examination indicated that the ventricles had significant interstitial edema. Accordingly, greater QRS voltage may be attributable to so-called enhanced ventricular mass effects at this stage. It has been shown that an increase in R waves is linked to heart function in situations of acute myocardial infarction (Kautzner and Malik, 1997). The S-T result after 2 weeks there is significant decrease at $P \leq 0.05$ between G2 doxorubicin as compared to G4 Eruca sativa + doxorubicin and G4. After 4 weeks there is no significant difference between all groups. within the group in G3 there is significant decrease in 4 weeks as compared to 2 weeks.

Table 1-6
The S-T Duration (ms) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	0.124±0.04 A a	0.124±0.04 AB a	0.124±0.02 A a	0.028 NS
G2- doxorubicin	0.124±0.04 A a	0.108±0.02 B a	0.112±0.03 A a	0.031 NS
G3 Eruca sativa	0.124±0.04 A ab	0.148±0.07 A a	0.100±0.02 A b	0.038 *
G4 Eruca sativa + doxorubicin	0.124±0.04 A a	0.148±0.05 A a	0.116±0.02 A a	0.034 NS
LSD value	0.030 NS	0.037 NS	0.033 NS	---

Means with different big letters in the same column and small letters in the same row are significantly different. * ($P \leq 0.05$).

Myocardial ischemia is indicated by ST-segment elevation. V3 and V4 always exhibit reciprocal ST-segment changes when compared to posterior leads V7–V9 (In one lead, ST elevation is followed by ST depression in the opposite lead). This is a particularly specific heart attack symptom. An upsloping, convex ST segment can effectively indicate a myocardial infarction (Pardee sign) on the other hand, a concave small ST elevation is less significant and can be found for causes other than ischemia. A ventricular aneurysm may form after infarction, and this might result in chronic ST elevation, loss of the S wave, and T wave inversion (de Blied, 2018). The Q-T duration result after 2 weeks refers to there being no significant difference between all groups. The Q-T result after 4 weeks refers to a significant decrease at ($P \leq 0.05$) G2 doxorubicin as compared to the control group. as well as there is no significant decrease at ($P \leq 0.05$) between G2 doxorubicin as compared to G4 *Eruca sativa* + doxorubicin and G3 *Eruca sativa*. Within the groups in G2 there is significant decrease in 4 weeks as compared to 2 week and zero time.

Table 1-7
The Q-T Duration (ms) in rabbits of each group after 0,2 and 4 weeks

Group	Period means			LSD value
	Zero time	2 week	4 week	
G1 Control	0.172±0.05 A a	0.172±0.05 A a	0.172±0.05 A a	0.031 NS
G2- doxorubicin	0.172±0.05 A a	0.168±0.04 A a	0.120±0.03 B b	0.040 *
G3 <i>Eruca sativa</i>	0.172±0.05 A a	0.172±0.05 A a	0.148±0.04 AB a	0.038 NS
G4 <i>Eruca sativa</i> + doxorubicin	0.172±0.05 A a	0.172±0.05 A a	0.160±0.04 AB a	0.022 NS
LSD value	0.033 NS	0.033 NS	0.041 *	---

A statistical analysis of the Q-T duration data revealed a decrease in the interval, which was associated with an increase in the intracellular cardiac Ca^{++} value. And the toxicity may also be brought on by an electrolyte imbalance in addition to increased intracellular calcium brought on by the suppression of the $\text{Na}^{+}\text{-K}^{+}$ ATPase pump (Salih, 2016). therefore one of the possible damages of sodium is that it may increase the chances of developing some diseases and health problems in the circulatory system, such as: heart muscle enlargement. Heart failure The reason for this potentially negative effect of sodium on the circulatory system is that sodium entering the body draws water from the body into the bloodstream, which can increase blood volume, which can lead to health complications (Nakamura *et al.*, 2022).

Electrocardiography (ECG)

Control group (2,4 weeks)

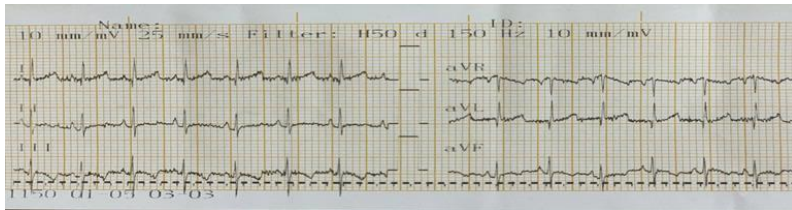


Figure 1-3. Group one control group (2 weeks)

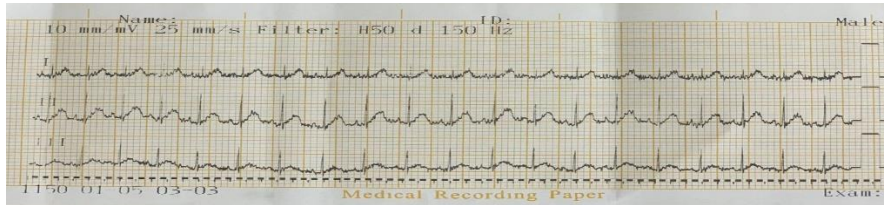


Figure 1-4. Group one control group (4 weeks)

Group Two Doxorubicin (2,4 weeks)

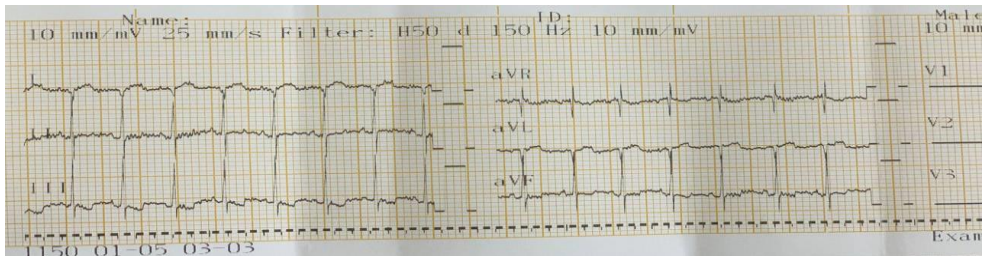


Figure 1-5. Group two (doxorubicin 2 weeks)

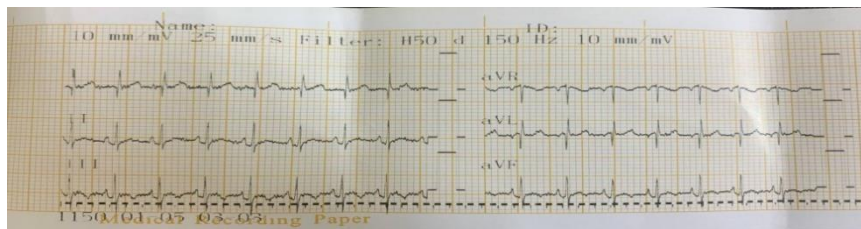


Figure 1-6. Group Two (Doxorubicin 4 weeks)

Group Three *Eruca sativa* mill (2,4 weeks)

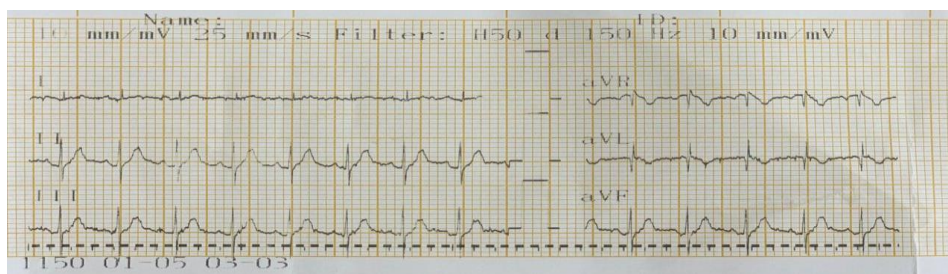


Figure 1-7. Group Three (*Eruca sativa* mill 2 weeks)

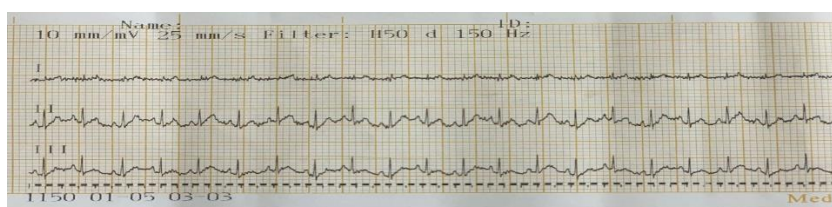


Figure 1-8. Group Three (*Eruca sativa* mill 4 weeks)

Group Four *Eruca sativa* + Doxorubicin(2,4 weeks)

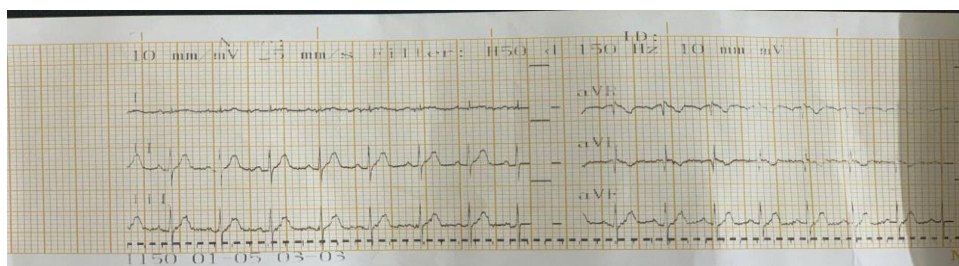


Figure 1-9. Group Four (*Eruca sativa* + Doxorubicin 2 weeks)

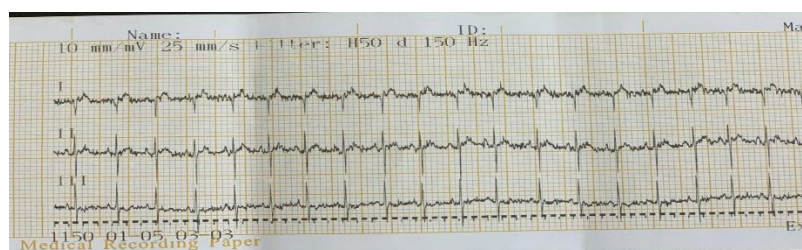


Figure 1-10. Group Four (*Eruca sativa* + Doxorubicin 4 weeks)

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