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Cardioprotective study of *Eriobotrya japonica* leaf extracts against carbon tetrachloride induced toxicity in rats

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ABSTRACT

The Rosaceae family includes the evergreen subtropical tree known as *Eriobotrya japonica* Lindl (loquat). To test the effect of several *E. japonica* leaf extracts on shielding the heart from carbon tetrachloride (CCl_4) cytotoxic effects, we employed carbon tetrachloride (CCl_4), a highly toxic chemical, to cause cardiotoxicity in rats. The heart function enzymes that were examined were lactate dehydrogenase (LDH) and Creatine Kinase. When compared to both the hazardous and normal groups, it was discovered that the protective dose of ethyl acetate extract (200 mg/Kg) and aqueous extract (100 and 200 mg/Kg) lowered the cardiac indicators. Total protein, malondialdehyde (MDA), and non-protein sulfhydryls (NP-SH) indicators were used to assess myocardial oxidative stress. Rats pretreated with ethyl acetate (200 mg/Kg) and aqueous extract (100 and 200 mg/Kg) showed higher levels of total protein than the control group. When compared to the silymarin group, all of the loquat leaf extracts examined in this study increased the amount of the MDA enzyme. The data also demonstrated that, when compared to the results from the normal group, aqueous extract (100 and 200 mg/Kg) enhanced the amount of NP-SH. The histopathology showed that administration of all loquat leaf extracts at doses of (100 mg/kg, 200 mg/kg) before CCl_4 intoxication greatly reduced the modifications that were exhibited by CCl_4 and preserved cardiac muscles that were very equivalent to those of normal control. Based on the aforementioned data, we deduced that loquat leaf aqueous extract provided the highest protection for heart tissue against the effects of CCl_4 intoxication. Through chemical examination of the methanolic extract, four flavonoids were extracted and identified. Their structures were found to be kaempferol-3-O-rhamnoside **1**, quercetin-3-O-rhamnoside **2**, quercetin-3,7 di-O-glycerides **3**, and roseoside **4**.

1. Introduction

The evergreen subtropical tree *Eriobotrya japonica* Lindl (loquat) belongs to family Rosaceae (Younes & Sassine, 2016). Chinese folk medicine used loquat plant in the treatment of many ailments (Liu et al., 2016), consequently different scientific studies was made on loquat plant proven some of its bioactivities such as anti-tumor(Ito et al., 2002), treatment of bronchial asthma (Hirota & Suganuma, 2009), anti-inflammatory (Cha et al., 2011); (Selvamuthukumaran et al., 2020), antioxidant (Delfanian et al., 2015), anti-diabetes(Suhani & Soubhik, 2018), cardio-protective(Chiang et al., 2018), anti-hyperglycemia (Ahumada et al., 2017) and hepatoprotective (Shahat et al., 2018).

E. japonica seeds and fruits are rich in alkaloids, cardiac glycoside, flavonoids, phenols, mucilage, phytosterol and gums(Ibrahim, 2021). Seeds and young leaves of loquat plant contain a small amount of cyanogenic glycoside which forms cyanide when digested so a great caution must be taken during use (Baljinder, Seena, Dharmendra, Vikas, & Bansal, 2010). Leaves were chemically investigated for their antioxidant effect. Due to the inclusion of various polyphenols, it was discovered upon fractionation that the ethyl acetate portion had the maximum antioxidant activity (Nawrot-Hadzik, Granica, Abel, Czapor-Irzabek, & Matkowski, 2017). Nitric oxide, COX2, and TNF- are powerfully inhibited by the butanol extract of E. japonica leaves. These inhibitors have analgesic and anti-inflammatory effects, making them useful in the therapy of many inflammatory illnesses (Cha et al., 2011).

An Ultra High Performance Liquid Chromatography connected with a quadrupole time of flight mass spectrometry (UHPLC-QTOF-MS) revealed that all loquat parts (stem, leaf, roots, seeds and fruits) are rich

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in polyphenols and terpenoids (Zhang et al., 2021). Polyphenols show a noticeable effect on coronary heart disease. Hepatic cholesterol and triglycerides are decreased by polyphenols this action protects from atherosclerotic process thus protecting the heart against coronary heart disease (Murillo & Fernandez, 2017; Portincasa & Calamita, 2019); as well as acting as a protecting agent against cardiovascular system aging (Khurana).

Ursolic acid is a triterpenoid and was isolated from loquat leaves (Tan et al., 2019). Ursolic acid provides a protective effect on heart (Balanehru & Nagarajan, 1992). Thus, ursolic acid was used as a therapeutic agent for prevention or decreasing the toxic effect of doxorubicin drug on the heart (Mu et al., 2019). Doxorubicin is an anthracycline antibiotic (Wouters, Kremer, Miller, Herman, & Lipshultz, 2005) which is used in the treatment of some tumors but has a very harmful effect on the heart (Thorn et al., 2011). The prevention or decrease of this harm effect on the heart will lead therapeutics to be able to use higher doses of doxorubicin and thus more cure percentages will be reached.

Previously, we have investigated the hepatoprotective activity of the total extracts and the different fractions of *Eriobotrya japonica* (Shahat, et al., 2018). In order to explore the impact of several *E. japonica* leaf extracts on shielding the heart from CCl_4's cytotoxic effects, we employed CCl_4, a highly toxic chemical, to induce cardiotoxicity in rats.

2. Material and methods

2.1. General experimental procedures

For column chromatography, Silica gel 60 (230–400 mesh, Merck Kieselgel) were used TLC analytical were performed on silica gel 60 F_{254} were used and visualized under UV light at 366 and 254 nm and /or using NA reagent or Vanillin sulphuric acid. Nuclear magnetic resonance spectra were recorded in deuterated methanol or deuterated dimethylsulfoxide (DMSO-d_6) Ultra Shield Plus system (Bruker Biospin GmbH, Rheintetten Germany) operating at 700 MHz for ^{1}H and at 175 MHz for ^{13}C NMR.

2.2. Collection and identification of the plant

In March 2019, leafy *Eriobotrya japonica* was collected from the Wadi Houf garden in Helwan, Egypt. The taxonomy was validated by Prof. Dr. Ibrahim EL-Graf, Professor of Taxonomy at Cairo University's Faculty of Science in Cairo, Egypt. Er-JA-SH-2019 was given as the reference number or voucher.

2.3. Plant extraction and isolation

The leaves were air dried and ground into a powder (985 g), and 80 % (v/v) methanol–water was used for extraction. After the solvent was removed under decreased pressure with rotary evaporator, the crude aqueous methanolic extract was obtained. One candidate for the hydromethanolic extract (Er-1) was the residual (112 g). The remaining aqueous was designed as (Er-4), and a portion of the residual Er-1 (80 g) was effectively defatted with hexane, fractionated with chloroform, ethyl acetate (Er-2), and n-butanol (Er-3) before being suspended in water. The butanol fraction (8 gm) was subjected to column chromatography on silica gel 60 eluted with $CHCl_3$ with increasing polarity with MeOH, provided to 10 fractions (Bu1-Bu10). Repeated column chromatography of fraction Bu-2 and Bu-3 led to the isolation of known compounds named kaempferol-3-O-rhamnoside and roseoside. These compound characterized and identified by comparing the data with literature (Diantini et al., 2012; Ito et al., 2002). Fraction Bu-5 and Bu-6 afforded compounds quercetin-3-O-rhamnoside and quercetin-3,7 di-O-glycerides respectively and identified by comparing the data with literature (Shahat et al., 2002) respectively.

2.4. Experimental animals

44 male Wistar rats weighing 180–20 g were used in this study. The rats were divided into groups at random and exposed to typical circumstances for roughly seven days at 25 °C with 12-hour light/dark cycles. All of the animals received free access to food and water while being subject to strict sanitary regulations. The animal experimentation ethics committee gave the project their blessing (approval number: 20–015 National Research Center, Egypt).

2.5. Experimental design

After receiving oral distilled water for 14 days, the first group, referred to as the "normal control," was administered 1.5 mL/kg of olive oil intravenously on the fourteenth day. Group II received treatment with CCl4 (1.5 mL/kg i. p.) diluted (1:1) with olive oil on the fourteenth day. Group II got oral distilled water for 14 days while serving as a toxic control group with CCl_4. Group III served as the positive control group. On the fourteenth day, two hours after receiving the last dose of silymarin, the animals were administered CCl4 (1.5 mL/kg i.p.) diluted (1:1) with olive oil. A silymarin extract in methanol at a dose of 10 mg/kg was administered orally for 14 days. Groups IV, V, VI, VII, VIII, IX, X, and XI received daily dosages of 100 and 200 mg/kg of various E. japonica extracts for 14 days. They were given CCl_4 (1.5 mL/kg i. p.) that had been diluted (1:1) with olive oil on the fourteenth day. After receiving CCl_4 therapy, all rats were killed 24 h later. Just before the sacrifice, blood was drawn.

2.6. Assessment of cardiac function markers in serum

After 24 h of CCl4 injection, blood samples from the *retro*-orbital plexus of all the rats were collected. Serum was separated by centrifugation at 3000 rpm for 15 min in order to measure a number of biochemical markers for the heart function tests. It was then put into eppendorf tubes that had already been labeled. Two biochemical indicators, lactate dehydrogenase (LDH) and creatinine kinase (CK), were studied. Whole animals were immediately put to death under light ether anesthesia after blood was taken. The next step was to extract heart samples, clean them with chilled normal saline, and prepare them for tissue biochemical evaluations (Yusufoglu et al., 2018).

2.7. Preparation of heart homogenate

Heart samples were obtained and homogenized in a chilled 0.15 M KCl solution using a motor-driven Teflon pestle. The homogenized tissues were then treated with ethylenediamine tetraacetic acid (EDTA, pH 7.4) and centrifuged at 12000 rpm for 20 min. The supernatants were used to estimate total protein, NP-SH, and malondialdehyde (MDA).

2.8. Biochemical investigation

2.8.1. Biochemical estimation of markers in heart homogenate

The levels of total protein (Utley, Bernheim, & Hochstein, 1967), malondialdehyde (Sedlak & Lindsay, 1968), and non-protein sulfhydryls (NP-SH) in tissue homogenates could be calculated using the methods previously mentioned. Using malondialdehyde (MDA) and non-protein sulfhydryls (NP-SH), the degree of oxidative stress was calculated. The procedure was as follows: 0.2 mL of tissues were kept in a separate test tube and incubated at 37 °C for an hour before 1 mL of 10 % trichloroacetic acid (TCA) and 1 mL of 0.67 % thiobarbituric acid (TBA) were added. The test tube was then heated to 95 °C and allowed to boil for five minutes. The tube was centrifuged after cooling. The absorbance of the supernatant was measured at 532 nm.

0.1 mL of the supernatant was suspended in tris buffer and 5–5′-dithiobis-(2 nitrobenzoic acid) (DTNB) for the determination of NP-SH, and the absorbance was immediately measured at 412 nm against a

Table 1
Effect of extracts on Cardiac function test treated with CCl_4.

Treatments	Dose mg/kg	LDH(U/l)		Creatine- Kinase(U/l)	
		Mean ± S. S	% Change	Mean ± S. S	% Change
Normal		169.66 ± 2.80		107.01 ± 4.09	
CCl_4		309.16 ± 6.03*** [a]		198.74 ± 4.97***[a]	
Silymarin + CCl_4	**10**	178.83 ± 5.17*** [b]	42.15	118.40 ± 2.80*** [b]	40.42
Er-1 + CCl_4	**100**	297.33 ± 4.32[b]	3.82	185.85 ± 5.20[b]	6.48
Er-1 + CCl_4	**200**	284.00 ± 5.05* [b]	8.14	178.35 ± 8.22[b]	10.25
Er-2 + CCl_4	**100**	242.33 ± 5.22*** [b]	21.61	151.97 ± 6.31*** [b]	23.52
Er-2 + CCl_4	**200**	198.50 ± 5.43*** [b]	35.79	134.59 ± 3.02*** [b]	32.27
Er-3 + CCl_4	**100**	203.16 ± 5.30*** [b]	34.28	136.69 ± 5.31*** [b]	31.22
Er-3 + CCl_4	**200**	179.33 ± 6.02*** [b]	41.99	130.39 ± 4.19*** [b]	34.38
Er-4 + CCl_4	**100**	302.83 ± 4.91[b]	2.04	195.44 ± 4.19[b]	–
Er-4 + CCl_4	**200**	280.00 ± 5.77** [b]	9.43	170.26 ± 6.72** [b]	14.32

All values reflect mean ± SEM. *p < 0.05; **p < 0.01; ***p < 0.001; ANOVA, followed by Dunnett's multiple comparison test. [a] As Comparatively to the control group. [b]As compared with CCl_4 only group.
1-CCl_4 group compared to Normal group, 2-Treated groups compared with CCl_4 group.

blank. The result of both NP-SH and MDA were stated as nmol/g.

0.1 mL of the supernatant was suspended in tris buffer and 5–5′-dithiobis-(2 nitrobenzoic acid) (DTNB) for the determination of NP-SH, and the absorbance was immediately measured at 412 nm against a blank. The result of both NP-SH and MDA were stated as nmol/g.

2.8.2. Cardiac histopathological study

The control and treatment rats were sacrificed at the end of the experiments. Samples of dissected hearts were dehydrated in escalating alcohol concentrations, fixed in 10 % neutral formalin, and then embedded in paraffin wax. Hematoxylin and Eosin was used to stain paraffin slices (5 μm thick) for histological investigation by light microscope (Olympus BX51 optical microscope) (Shahat et al., 2022).

2.9. Statistical analysis

The one-way analysis of variance (ANOVA) or Student's *t*-test, followed by Dunnett's multiple comparison tests, were used to statistically examine the data. The information is presented as mean standard deviation (SD). The level of significance for statistical analysis was set at 0.05, 0.01 or 0.001.

3. Results

3.1. Several E. japonica extracts' effects on serum cardiac function markers

Table 1 displays the effects of different *E. japonica* extracts on cardiac function markers in CCl_4-intoxicated rats. LDH and creatine kinase levels in CCl_4-intoxicated rats were substantially (p 0.001) greater (309.166.03 and 198.744.97 U/I, respectively) than in control animals (169.662.80 and 107.014.09 U/I, respectively). The administration of the butanol fraction (Er-3) at doses of 100 and 200 mg/kg and the ethyl acetate fraction (Er-2) at doses of 200 mg/kg significantly (p 0.05–0.001) protected the heart and decreased the amount of elevated LDH and Creatine kinase levels in comparison to the CCl_4 group (toxic control).

3.2. Impact of several E. japonica extracts on myocardial oxidative stress indicators

The levels of total protein, MDA, and NP-SH in the cardiac tissues are shown in Figs. 1-3 (oxidative stress profile). Rats intoxicated with CCl4 had significantly lower levels of total protein than the control group (p 0.001) (Fig. 1). The amount of total proteins significantly increased (p 0.001) in the ethyl acetate extract (Er-2) (200 mg/kg), aqueous extract (Er-4) (100 and 200 mg/Kg), and silymarin (10 mg/kg) groups. In rat cardiac tissue, MDA in the CCl4-impaired group was larger (4.55 nmol/g) than in the normal group (0.67 nmol/g) (p 0.001). The substantial (p 0.05–0.001) protective level of MDA (Fig. 2) was high for all tested

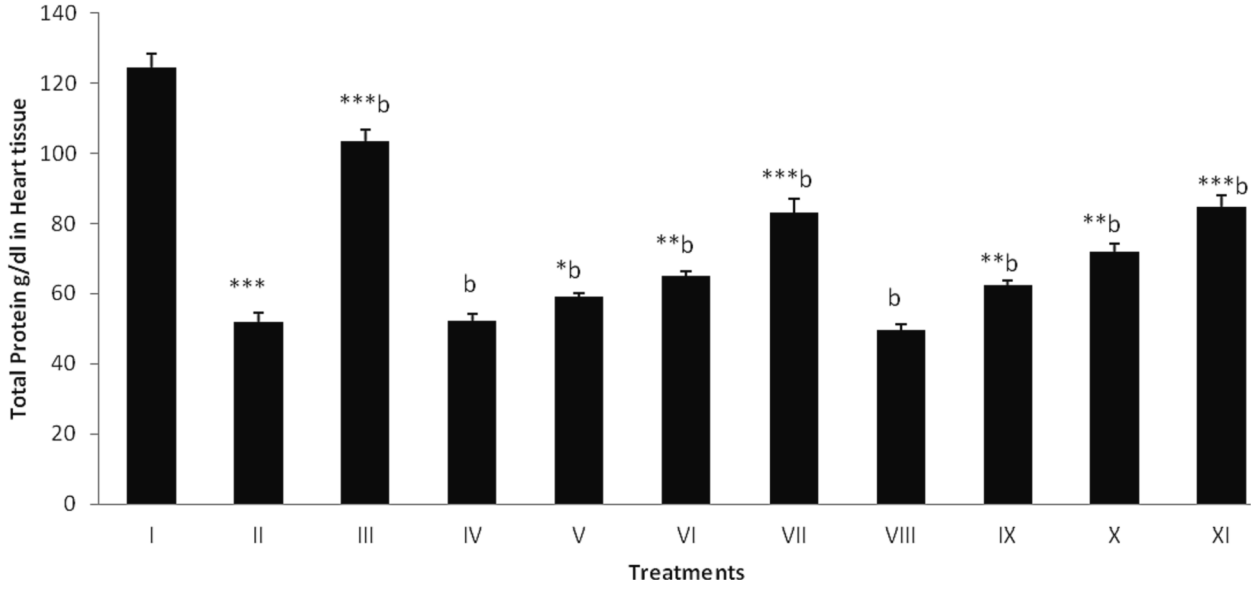


Fig. 1. Effect of extract fraction on Total Protein in Heart tissue. The mean SEM is used to express all values. Following the ANOVA, Dunnett's multiple comparison test is applied; * p 0.05, *** p 0.001. When contrasting groups, a and b with the Normal group, I = Normal, II = CCl_4, III = Silymarin + CCl_4, IV = ER-1 (100 mg/kg) + CCl_4, V = ER-1 (200 mg/kg) + CCl_4, VI = ER-2 (100 mg/kg) + CCl_4, IX = ER-3 (200 mg/kg) + CCl_4, X = ER-4 (100 mg/kg) + CCl_4, XI = ER-4 (200 mg/.

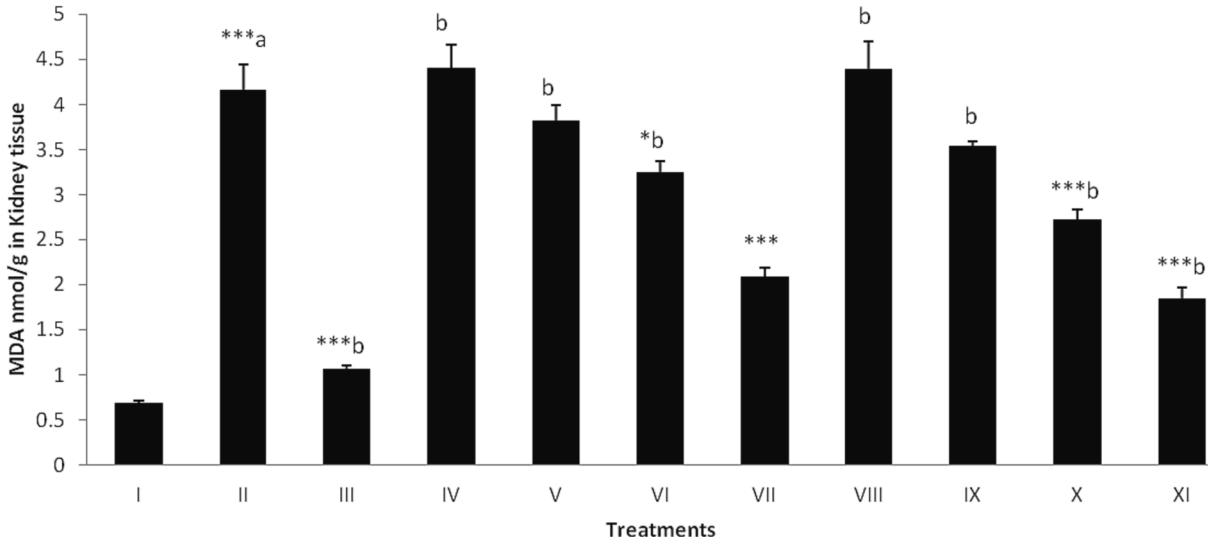


Fig. 2. Malondialdehyde (MDA) effects of extract fraction in heart tissue. All values are expressed as mean SEM. * p 0.05 *** p 0.001; Dunnett's multiple comparison test is used after the ANOVA. Where a and b are comparisons to the Normal group and a group, respectively. I-Normal, II -CCl_4, III- Silymarin + CCl_4, IV- ER-1(100 mg/kg) + CCl_4, V- ER-1(200 mg/kg) + CCl_4, VI- ER-2 (100 mg/kg) + CCl_4, VII- ER-2 (200 mg/kg) + CCl_4, VIII- ER-3 (100 mg/kg) + CCl_4, IX- ER-3 (200 mg/kg) + CCl_4, X- ER-4 (100 mg/kg) + CCl_4, XI- ER-4 (200 mg/kg) + CCl_4.

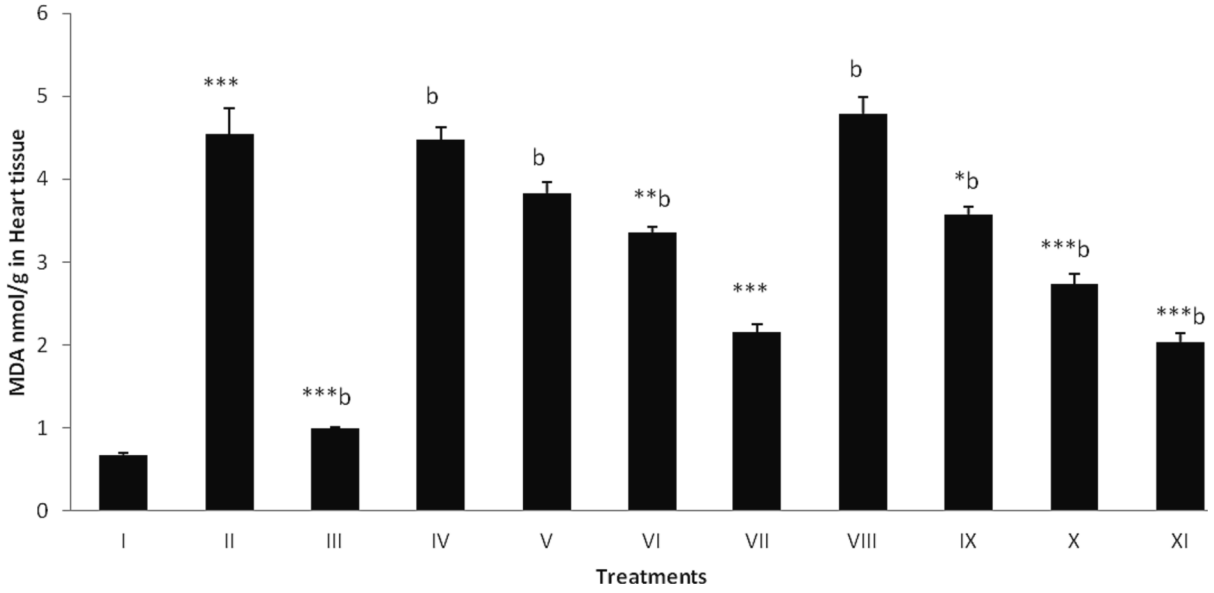


Fig. 3. Effect of extract fraction on heart tissue's NP-SH (non-protein and sulfhydryls). The mean SEM is used to express all values. Following the ANOVA, Dunnett's multiple comparison test is applied; * p 0.05, *** p 0.001. In which the Normal group was contrasted with groups a and b. I-Normal, II -CCl4, III- Silymarin + CCl4, IV- ER-1(100 mg/kg) + CCl4, V- ER-1(200 mg/kg) + CCl4, VI- ER-2 (100 mg/kg) + CCl4, VII- ER-2 (200 mg/kg) + CCl4, VIII- ER-3 (100 mg/kg) + CCl4, IX- ER-3 (200 mg/kg) + CCl4, X- ER-4 (100 mg/kg) + CCl4, XI- ER-4 (200 mg/kg) + CCl4.

samples as compared to the silymarin (10 mg/kg) group. We found that the aqueous extract groups (Er-4) at doses of 100 and 200 mg/Kg offered the best outcomes when comparing the NP-SH results (Fig. 3) to the silymarin group. The NP-SH level in CCl4 (2.52 nmol/g) was significantly (p 0.001) lower than that of the rats in the normal (5.72 nmol/g) groups. When given at doses of 100 and 200 mg/kg each, silymarin and the aqueous extract considerably (p 0.05–0.001) protected the heart tissues.

3.3. Cardiac histopathology

Light microscopy examination of heart tissue in a control rats show normal architecture of cardiac muscle fibers (Fig. 4A). The heart's usual radiating pattern of cell plates was disrupted by CCl4 therapy. Vast regions of necrotic muscle fiber and clogged blood arteries were discovered (Fig. 4B).(See Fig. 5).

Silymarin and CCl_4-treated rats showed nearly normal cardiac structure that represented by less disorganization of normal radiating pattern of cell plates in the heart. Foci of necrotic areas of muscle fiber and no congested blood vessels were found (Fig. 4C).

Administration of the Er-1, Er-2, Er3, and Er-4 (100 mg/kg, 200 mg/kg) extracts before CCl_4 intoxication markedly reduced the changes that exhibited by CCl_4 and kept heart muscles quite similar to that of normal control ((Fig. 4D, 4E, 5A. 5B, 5C, 5D, 5E, 5F respectively).

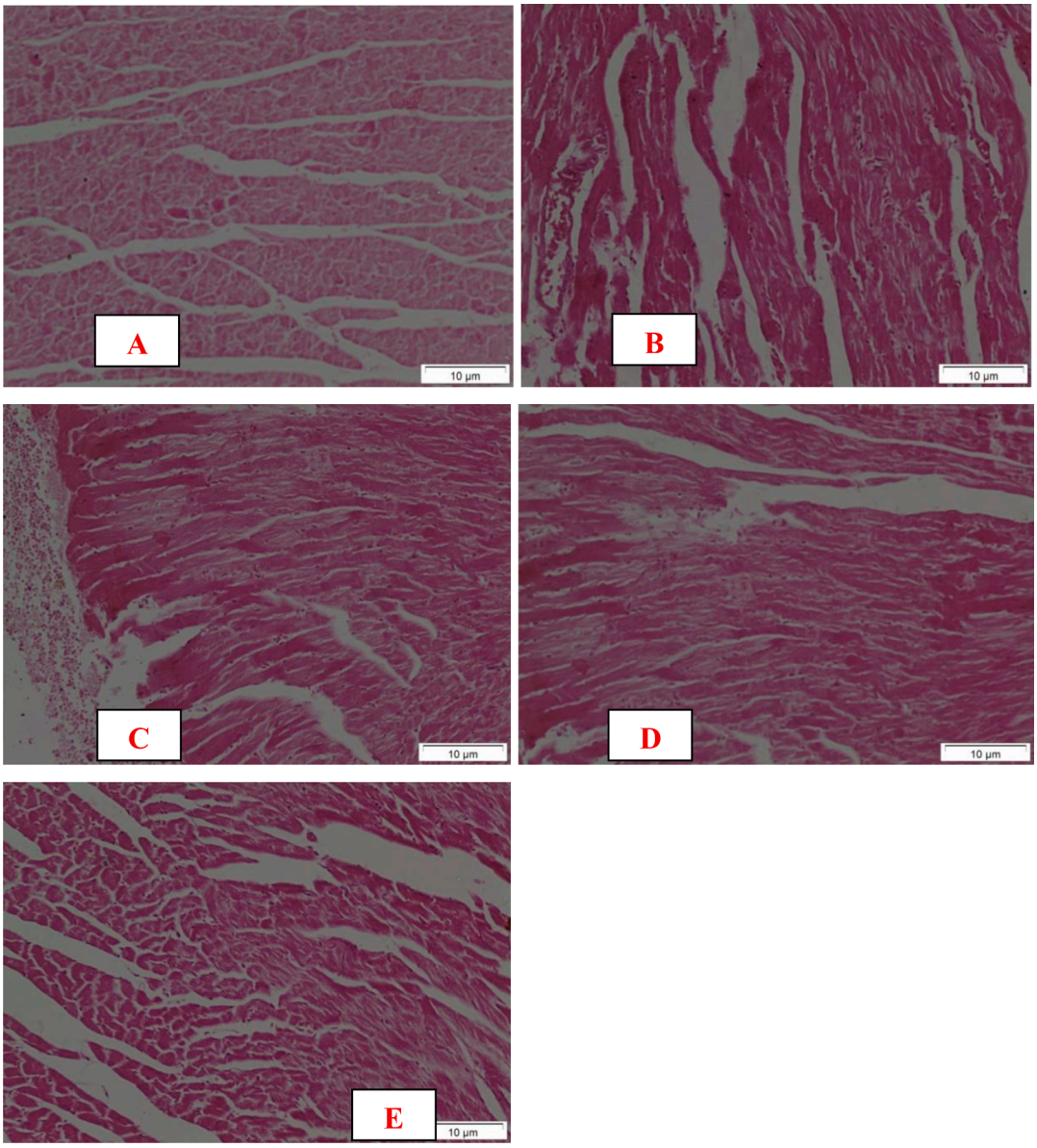


Fig. 4. A micrograph of heart from A) rat of normal group, B) rat of CCl_4 group, C) rat of Silymarin and CCl_4 group, D) rat of Er-1–100 mg/kg and CCl_4 group, E) rat of Er-1–200 mg/kg and CCl_4 group (H & E, Scale Bar: 10 µm).

4. Discussion

Our study emphasized the improving effect of loquat extracts on cardiac tissue toxicity. This could be due to the high antioxidant activity of loquat (Delfanian et al., 2015; Koba et al., 2007). From previous studies it was found that *E. japonica* has a good effect on cardiac health. A study made by Chiang (Chiang et al., 2018) reveled that *E. japonica* leaf extract improved myocardial apoptosis and fibrosis in rats with hypertension induced- heart failure. It was found that loquat plant also has positive effect on muscle strength (Cho et al., 2016) and thus improves the heart muscle.

E. japonica is rich in polyphenols (Zhang et al., 2021; Zhang et al., 2015) and terpenoids (Zhang et al., 2021). Polyphenols show a noticeable effect on coronary heart disease. Hepatic cholesterol and triglycerides are decreased by polyphenols this action protects from atherosclerotic process thus protecting the heart against coronary heart disease (Murillo & Fernandez, 2017; Portincasa & Calamita, 2019). Polyphenol compounds are known to be helpful for cardiovascular health; as well as acting as a protecting agent against cardiovascular system aging (Khurana). All these find agreed with our current research where we have not only identified the phenolic compounds but also finding out the cardioprotective effect of *E. japonica*. Previously researchers also isolated ursolic acid (a triterpenoid) from loquat leaves (Tan et al., 2019) which have the potential of protective effect on heart (Balanehru & Nagarajan, 1992). Thus, ursolic acid was used as a therapeutic agent for prevention or decreasing the toxic effect of doxorubicin drug on the heart (Mu et al., 2019). The isolation of cardipreotcive consituents from plants is the demand of present time. There are many drugs used for the treatment of some disease have adverse effect on heart (Wouters et al., 2005; Thorn et al., 2011). The prevention or decrease of this harmful effect on the heart require to isolate more and more novel therapeutics agents with no or less side effects. In our study the aqueous extract of loquat was the most effective part on improving cardiac induced-toxicity.

As Previously already by researchers that Loquat comprised of active constituents such as flavonoids, tannins terpenoids, phenols and that have the ability of protective effect (Ibrahim 2021). These compounds might be a source for the cardioprotective effect of *E. japonica*.

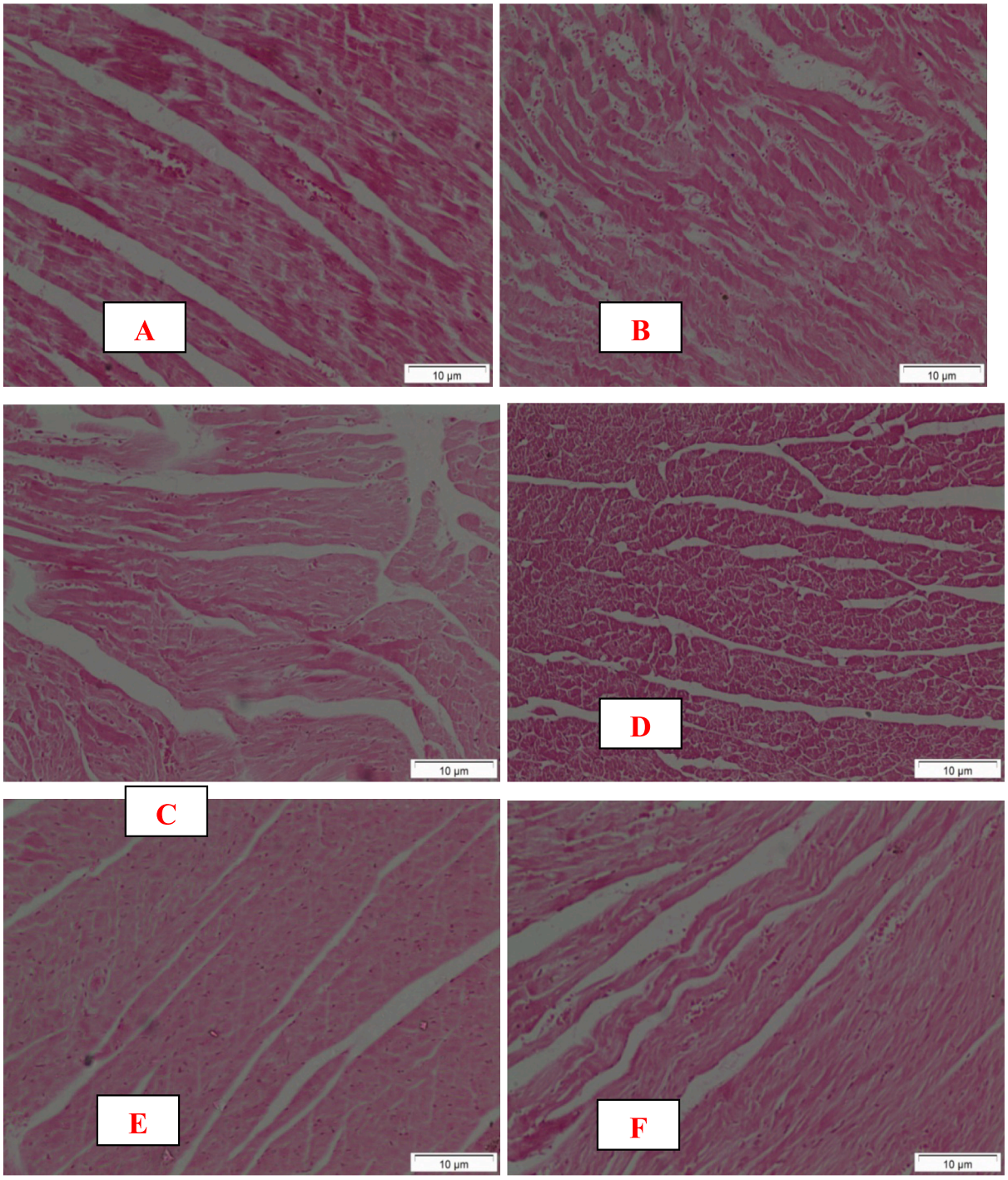
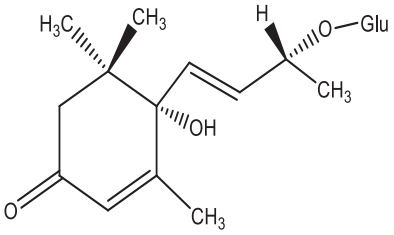


Fig. 5. A micrograph of heart from A) rat of Er-2–100 mg/kg and CCl_4 group, B) rat of Er-2–200 mg/kg and CCl_4 group, C) rat of Er-3–100 mg/kg and CCl_4 group, D) rat of Er-3–200 mg/kg and CCl_4 group, E) rat of Er-4–100 mg/kg and CCl_4 group, F) rat of Er-4–200 mg/kg (H & E, Scale Bar: 10 µm).

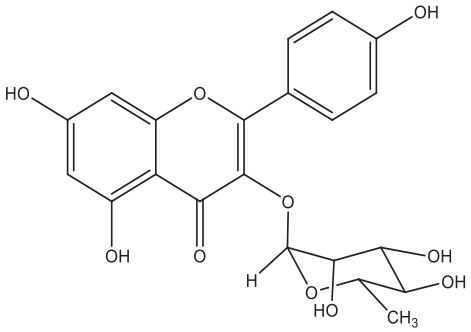
Furthermore, the aqueous extract of some plants also reporting protective effect against myocardial damage (Shackebaei et al., 2017; Sadeghi et al., 2015; Nwokocha et al., 2017). These finding agree with our current find of aquoses extract protective potential.

5. Conclusion

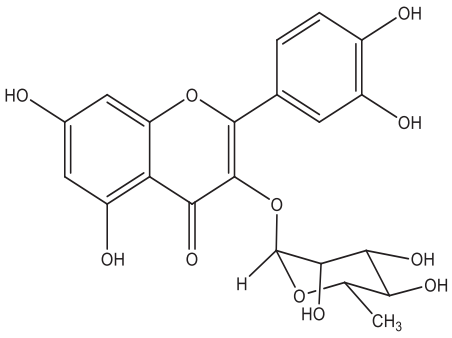
The administration of all loquat leaf extracts in doses of (100 mg/kg, 200 mg/kg) before CCl_4 intoxication clearly minimized the alterations demonstrated by CCl_4 and retained heart muscles very comparable to that of normal control, according to histopathology. Based on the aforementioned data, we deduced that loquat leaf aqueous extract provided the highest protection for heart tissue against the effects of CCl_4 intoxication. The cardioprotective potential of loquat leaf extracts open a window for researcher to isolate phytoconstituents responsible for cardioprotective potential of loquat leaf extracts.



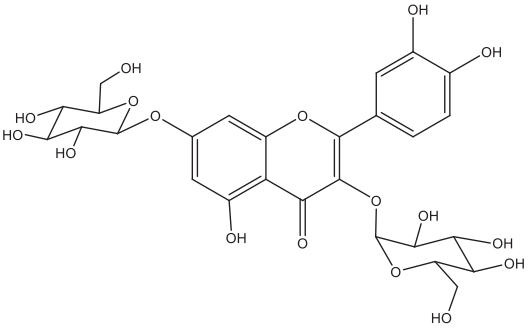
Roseoside



Kaempferol-3-O-rhamnoside



quercetin-3-O-rhamnoside



quercetin-3,7 di-O-glycerides

Chemical Structure of the isolated compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contribution

All authors contributed equally.

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