Minufiya J. Agric. Res. Vol.40 No. 5: 1323 – 1338 (2015) **"http://www.mujar.net"**

CARDIOPROTECTIVE EFFECTS OF *Lagenaria Sicessaria* (Molina) FRUIT JUICE AGAINST ISOPROTERENOL AND CARBON TETRACHLORIDE INDUCED-MYOCARDIAL INFRACTION IN ALBINO RATS

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(Received: Aug. 18 , 2015)

ABSTRACT: *The present study was designed to evaluate the cardioprotective effects of Lagenaria siceraria fruit juice in carbon tetrachloride (CCl_4) and isoproterenol (ISO)-induced Cardiotoxicity infraction. Rats injected with isoproterenol (85 mg/kg, s.c.) induced a significant decrease in total protein, catalase, GPx and HDL showed a significant increase in the levels of serum uric acid, Na, Ca, creatinine, urea, serum total cholesterol, triglycerides, LDL, GOT, GPT and ALP. Isoproterenol and CCl_4 injected rats also showed a significant when $P \leq 0.05$ increased incidence of DNA fragmentation and apoptosis which were evident in pups of isoproterenol and CCl_4 injected. Treatment with L. siceraria fruit juice (30 ml/kg/day, p.o.) and administration of isoproterenol and CCl_4 showed a protective effect on altered biochemical and showed a marked amelioration in DNA. These findings indicate the cardioprotective effect of L. siceraria fruit juice in CCl_4 and isoproterenol-induced myocardial infraction in rats.*

Key words: *Carbon tetrachloride (CCl_4), isoproterenol, Lagenaria siceraria, myocardial infraction*

INTRODUCTION

Carbon tetrachloride (CCl_4) is a well-known model compound for producing chemical tissue toxicity by generation of free radicals in many tissues (Adaramoye, 2009) such as liver, kidneys, heart, lung, testis, brain and blood (Ahmad *et al*., 1987 and Ozturk *et al*., 2003). It is biotransformed by hepatic microsomal cytochrome P450 to trichloromethyl-free radical ($CCl_3^{\bullet}$ or $CCl_3OO^{\bullet}$) (Shenoy *et al.,* 2001), which in turn, initiate lipid peroxidation process (Adewole *et al.,* 2010). The most widely accepted mechanism of CCl_4 induced cardiotoxicity is the formation of free radicals which is a rate limiting process in tissue peroxidative damage (Plaa and Witschi, 1976). This free radical related to reactive species may cause oxidative stress, which produces major interrelated rearrangements of cellular metabolism, increase in intracellular free calcium, damage to membrane ion transport and permeability, and destruction of the cells by lipid peroxidation (Giordano, 2005). The accumulating of lipid peroxides introduces hydrophophilic moieties hydrophobic phase and thus alter membrane permeability and cell function. This leads to loss of myocardial structural integrity and depressed cardiac function resulting in cardiotoxicity and congestive cardiac failure (Plaa and Witschi, 1976).

Isoproterenol (ISO) induced myocardial injury in rats has been shown to be accompanied by hyperglycemia, hyperlipidemia, increase in serum creatine phosphokinase, alanine aminotransferace, aspertate aminotransferase and lactate dehydrogenase activities (Purvis *et al*., 1993).

The edible portion of fruits is considered as a source of ascorbic acid, beta carotene and good source of vitamin B complex, pectin dietary soluble fibers and contains highest source of choline level-anisotropic factor (Nadakarni and Nadakarni, 1992). Modern phytochemical screening methods showed the presence of cytotoxic triterpenoids D:C-Friedooleanane (Chen *et al.,* 2008), bryonolic acid an antiallergic

compound (Tabata *et al.,* 1993) and flavone C-glycosides (Baranoswka and Cisowski, 1994). Lagenin, a novel ribosome inactivating protein has been isolated from the lyophilized water extract of seeds which is known to possess immunosuppressive, antitumor, antiviral, antiproliferative and anti-HIV activities (Wang and Ng, 2000). A water soluble cytotoxic polysaccharide, isolated from fruit of *L. siceraria* is composed of methyl-*α*-D-galactuoronate 3-*O*-acetyle methyl-*α*-D-galacuoronate and *β*-D-galactose (Ghosh *et al.,* 2009), polyphenol compounds (Rajput *et al*., 2011 and Jaiswal and Kuhnert, 2014).

Pharmacological properties of the herb include hepatoprotective, diuretic activity, antioxidant, antihyperglycemic immunomodulatory, antihyperlipidemic, cardiotonic, diuretic, antibacterial, analgesic, anti-inflammatory, cardioprotective, anti ulcer, anticestodal urolithiatic, antihypertensive, fibrinolytic, antiplatelet aggregation, antithrombotic and antihelminthic activity (Ghule *et al.,* 2006a; Ghule *et al.,* 2007; Deshpande *et al.,* 2008; Fard *et al.,* 2008;Upaganlawar and Balaraman 2009 and Rajput *et al*., 2013).

Maintaining the balance between reactive oxygen species and natural antioxidants is therefore crucial, and could serve as a major mechanism in preventing damage by oxidative stress induced by toxic agents (Türkdoğan *et al.,* 2001).

Till date, no study has been carried out regarding the effect of LSFJ on DNA induced by ISO and CCl_4. So, an attempt was made to evaluate the cardioprotective activity of LSFJ in CCl_4 and ISO-induced MI by evaluating biochemical and histopathologic changes discussed below.

MATERIALS AND METHODS

1. Drugs and chemicals

(±)-ISO hydrochloride was procured from Sigma Chemicals (St Louis, MO, USA). Fresh fruits of *L*. *siceraria* were farmed and collected from nearby farm at El-shohada – Monufia governorate- Egypt. Chemical kits used in this study were purchased from El-Gomhoria Company for Chemicals and Drugs, El-Ameria, Cairo, Egypt.

Isoproterenol was dissolved in normal saline and injected subcutaneously to rats (85 mg/kg) daily for 2 consecutive days to induce experimental myocardial infarction (Rajadurai and Prince, 2007 and Panda *et al.,* 2008).

Carbon tetrachloride CCl_4 was obtained from El-Gomhoria Company for Med-Preparations, Chemicals and Medical Equipments, Cairo, Egypt as 10% liquid solution. It was dispensed in white plastic bottles each containing one liter as a toxic chemical material for liver poisoning according to Jayasekhar *et al.,* (1997).

2. Preparation of *Langenaria siceraria* fruit juice

Fresh juice of *Langenaria siceraria* was prepared with the help of a juicer without adding water. The juice was filtered with a sterile cloth and the resultant filtrate was used for oral dosing to animals.

3. Experimental animals:

Seventy five adult male albino rats of an average weight 120±10 g and age (3 months), Sprague drawly strain, which fed on basal diet for one week. The basal diet consisted of 100 g/kg corn oil; 126.3 g/kg casein; 40 g/kg mineral mixture, USP XIV; 10 g/kg vitamin mixture; 3 g/kg DL-methionine and 2 g/kg choline chloride and 50 g/kg fiber and corn starch 668.7 g/kg according to AIN, (1993).

Then, rats divided into pre-test 40 rats and 35 divided into seven groups with similar total body weight and were housed individually in the wire cage.

4. Fixation of optimum dosage of *Langenaria siceraria* fruit juice (LSFJ):

A pilot study was carried out to establish the optimum dose of the drugs which exhibits maximum cardioprotective effect during 30 days, infected with CCl_4 and ISO was administered on 29^{th} and 30^{th} days. At the end of treatment period; 30 ml/kg /day,

p.o. was found to be the most effective dosage of LSFJ in functional recovery and this dose was selected for further evaluation in the present study.

5. Experimental design

The rats were divided into main seven group, control group (1) fed on basal diet as a (control negative); Group2 (Yaqtin) fed on basal diet an (LSFJ) 30 ml/kg, p.o.; Group 3 (positive liver control Group CCl_4) fed on basal diet and injected with CCl_4 ;Group 4 (Treated liver Group) inject with CCl_4 and then fed oral with (LSFJ) 30 ml/kg, p.o; Group 5(Protected liver Group) fed on basal diet and fed oral with (LSFJ) 30 ml/kg, p.o. for three weeks then injected with CCl_4 Group 6 (positive heart control Group ISO) were administered with Isoproterenol; Group7 (Protected heart Group) were pretreated with *Lagenaria siceraria* fruit (LSFJ) (30 ml/kg, p.o. body weight, respectively) for a period of 30 days and then administrated with isoproterenol at the end of the treatment period on the 31st and 32nd day. At the end of experimental period (on the day 33), blood samples were collected and animals were killed. A heart tissue sample of each rat was collected.

6. Biochemical evaluation:

At the end of experiment period (33 days), blood samples were collected after 12 hours fasting in a clean dry centrifuge tubes and left to clot at room temperature, then centrifuged for 10 min at 3000 rpm to separate the serum. Serum was carefully a separated, transferred in to clean cuvette tubes, and stored frozen at -20^{o}C for analysis.

Serum samples were analyzed for determination the following parameters: Glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) according to Yound, (1975) and Tietz, (1976), and alkaline phosphatase (ALP) according to Belfield and Goldberg, (1971), superoxide dismutase (SOD) according to Sun *et al.*, (1988), Glutathione Peroxidase (GPX) according to Zhao, (2001), Catalase according to Diego, (2011).

At the same time, the organs: heart, liver, kidney, lungs and spleen were removed, dried by filter paper, weighted, and liver divided into two group (1) stored frozen as it for DNA testing; group (2) stored frozen in formalin solution 10% for histopathological tasting according to method mentioned by Bancroft *et al*., (1996).

7. Determination of DNA fragmentation

Extraction of DNA was done according to the method of Aljanabi and Martinez (1997); and Hassab El-Nabi, (2004). Briefly, biopsies of freshly eye specimens weighing 10 mg were squeezed in Eppendorf tubes, lysed with 600 µL buffer (50 mmol/L NaCl, 1 mmol/L Na2EDTA, 0.5% sodium dodecyle sulphate (pH 8.3) and shacked gently. The mixture was incubated overnight at 37°C. For protein precipitation, an amount of 200 µL of saturated NaCl was added to the samples, shacked gently and centrifuged at 12000 r/min for10 min. The supernatant was transferred to new Eppendorf tube and the DNA was precipitated by 600 µL cold iso-propanol. The mixture was inverted several times till fine fibers of nucleic acids appeared, at which time the mixture centrifuged for 5 min at12000 r/min. The supernatant was then removed and the pellets (DNA and RNA) were washed with 500 µL 70% ethanol and centrifuged at 12000 r/min for 5 min. The supernatant was decanted and the tubes were plotted on Whatman paper to dry for 10 min. The pellets were re-suspended in 50 µL of Tris-EDTA buffer (10 mmol/L Tris, 1 mmol/L EDTA, pH 8).The re-suspended DNA was incubated for 30-60 min with loading mix (Rnase + loading buffer) and then added into the agarose gel wells. A gel was prepared with 2% electrophoretic grade agarose containing 0.1% ethidium bromide (200 µg/mL). The DNA samples were mixed with loading buffer (0.25% bromophenol blue, 0.25% xylene cyanole FF and 30% glycerol) and loaded into the wells (2 µg of DNA/lane) with a standard molecular-sized ladder marker (Pharmacia Biotech., USA). The gel was electrophoresed at a current of 50 volt for 1h using the submarines gel electrophoresis machine. The DNA was

visualized and photographed with illumination under ultraviolet light using a photo-documentation hood (Fisher Scientific, Pittsburgh PA, USA) equipped with a Polaroid 667 film with an orange filter (Kodak, Rochester, NY, USA). The ultraviolet reacts with the ethidium bromide to show the DNA fragments. Apoptotic bands appeared and located at 200 bp and its multiples.

8. Statistical Analysis

The experimental data were subjected to an analysis of variance (ANOVA) for a completely randomized design using a statistical analysis system (SAS, 2000). Duncan's multiple range tests were used to determine the differences among means at the level of 95%. Differences between treatments of $p \leq 0.05$ were considered significant.

RESULTS AND DISCUSSION

1. Effect of feeding *lagenaria-siceraria* juice on some blood biochemical parameters.

Table (1) showed the mean value of Na for rats feeding on *lagenaria-siceraria* fruit juice. It could be observed that the mean values of Na of treated groups with CCl_4 and ISO were significantly higher than negative control group and Yaqtin group, which being 185.85±3.91, 191.476±6.6, 158.15±0.94 and 155.25 ±1.21 mol/L respectively. Rats administered orally LSFJ as protective or treatment for (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) groups revealed that significant decreases in mean value as compared to treated groups with CCl_4 and ISO only. The values were 170.94 ±2.06, 159.74 ± 0.34 and 166.1±5.12 mol/L respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. There is no significant change between negative control group and Yaqtin group. The best mean value of Na was record for protective group (Pro+ CCl_4).

In the same table, the mean value of Ca rats feeding *lagenaria-siceraria* fruit juice. It could be observed that the mean value of Ca of treated groups with CCl_4 and ISO were higher than negative control group and Yaqtin group, the results was statically significant. The mean value were 4.63 ±0.42; 4.21±0.109 and 3.5±0.056; 3.32±0.21 mol/L for the above results respectively. Rats administered orally LSFJ in both of protective and treatment cases with CCl_4 and treatment case for ISO revealed significant decreases in mean value as compared to its positive groups. The mean values were 3.856±0.12, 3.58±0.072and 3.77±0.10mol/L respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. Tr+ CCl_4 group showed non significant differences with Tr+ISO group. The best mean value of Ca was protective (Pro+ CCl_4) group.

Table (1): Effect of feeding *lagenaria-siceraria* juice on minerals (Na, Ca) *(mol/L)* of rats.

Groups	Na(mol/L)	Ca(mol/L)
	Mean ±SD	Mean ±SD
Control(-)	158.15 ^{d}±0.94	3.5d^{e} ±0.056
Yaqtin	155.25 ^{d}±1.21	3.32^{e} ±0.21
CCl_4	185.85 ^{a} ±3.91	4.63 ^{a} ±0.42
Tr+ CCl_4	170.94 ^{b} ±2.06	3.856 ^{c}±0.12
Pro+ CCl_4	159.74 ^{cd}± 0.34	3.58 ^{cde}±0.072
ISO	191.476 ^{a}±6.6	4.21 ^{b} ±0.109
Tr+ISO	166.1 ^{bc}±5.12	3.77 ^{cd} ±0.10
LSD: P ≤ 0.05	6.492	0.3085

Means in the same column with different litters are significantly different at ($p \leq 0.05$).

Similar results were obtained by Upaganlawar and Balaraman (2010a) who found that the cardioprotective effects of *Lagenaria siceraria* fruit juice which significantly increased the levels of serum uric acid, tissue Na and Ca ions and membrane-bound Ca^{+2} -ATPase activity. Panda and Kar, (2011) isolated periplogenin-3-*O*-D-glucopyranosyl (1→6)(1→4)-D-cymaropyranoside, from the *Lagenaria siceraria* which led to decrease in cardiac Na (+)-K (+)-ATPase activity as well as serum total cholesterol.

2. Effect of feeding *lagenaria-siceraria* juice on catalase, GPx, total protein (TP) and uric acid (UA) of rats.

Data illustrates in Table (2), the mean value of GPx (ng/mL) of rats feeding of toxic groups by CCl_4 and ISO were lower than negative control group, which were 10.21 ±3.36, 19.06±0.138 and 32.886±5.17 (ng/mL) respectively, the results showing significant difference between CCl_4 and ISO groups as compared to negative control group. There are no significant changes between CCl_4 group and ISO group. Rats administered orally LSFJ as protective or treatment (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) revealed significant increases in mean value as compared to both negative control groups. The values were 17.17±2.53, 28.76 ±1.058 and 29.126±0.27 ng/mL respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. The best effect for LSFJ on GPx (ng/mL) was recorded for (Tr+Iso) group.

In case of the mean value of catalase (Mmol/L), it could be noticed that the mean value of catalase (Mmol/L) of positive control groups (CCl_4 or ISO) were lower than negative control group. While, administereting orally LSFJ led to significant increasing in mean value as protective or treatment from CCl_4 and treatment from ISO when compared to toxic groups CCl_4 and ISO only.

For the mean value of T.P (mg/dl), rats feeding LSGJ. It could be noticed that the mean value of T.P (mg/dl) of toxic groups CCl_4 and ISO was lower than control group, being 3.42±0.085; 3.35±0.145and 6.16±0.13 mg/dl respectively, showing significant difference decreased of toxic groups CCl_4 and ISO as compared to control group. Rats administered orally LSFJ protective or treatment (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) revealed significant increases in mean value as compared to toxic groups CCl_4 and ISO. The values were 5.19±0.00, 5.51±0.205 and 5.42±0.335 mg/dl respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. Rats on CCl_4 group and ISO group showed no significant differences between them. Rats on Tr+ CCl_4 group; Pro+ CCl_4 group and Tr + ISO showed no significant differences between them. The best T.P (mg/dl) was recorded for group (Pro+ CCl_4) when compare with control.

From the same table, It could be noticed that the mean value of U.A (mg/dl) of positive control groups (CCl_4 group or ISO group) were significantly higher than negative control group and Yaqtin group, which being 3.20±0.081; 3.203±0.081; 1.406±0.172 and 1.23 ±0.026 mg/dl respectively. There is no significant between both the positive groups, also there is no significant among Tr+ CCl_4 group, Pro+ CCl_4 group and Tr+ISO group. The above groups revealed significant decreases in mean value as compared to positive groups with CCl_4 or ISO.

The result of Shirwaikar and Sreenivasan (1996) was in the same line with the obtained results which reported a hepatoprotective activity was assessed by examining the influence of the extract of *Lagenaria siceraria* (EELS) and a significant increase in the level of glutathione. Also, Dixit *et al.* (2008) reported that feeding on *Lagenaria siceraria led to* increase in antioxidants level such as superoxide dismutase, catalase, and glutathione. Deshpande *et al*. (2008) showed a significant increase in the level of glutathione ($p \leq 0.05$) and non significant increased in superoxide dismutase.

Upaganlawar and Balaraman (2010b) who treated with ISO (200 mg kg^{-1}, s.c.) for two consecutive days at an interval of 24 h resulted in a significant ($p \leq 0.001$) alteration in antioxidants activity (reduced glutathione, glutathione peroxidase, glutathione s-transferase, superoxide dismutase and catalase). Vijayakumar *et al.* (2011) reported isoproterenol induced rats showed a significant fall in activities of enzymatic antioxidant likes SOD, CAT, GR and GSH. Katarea *et al.* (2013) found that administration of *Lagenaria siceraria* juice contributed to significant elevation in superoxide dismutase and catalase activities in both diabetic (40.5%) as well as normal healthy subjects.

The obtained result showed a decrease in total protein and increase in uric acid in CCl_4 and ISO groups, which matched with the previous reports of Rajadurai *et al.* (2007) showed that uric acid is an important independent risk factor for cardiovascular mortality and in the development of MI. McCord (1988) reported that ISO and CCl_4 elevated the levels of serum uric acid in injected rats and a decrease in the level of serum total proteins in ISO injected rats due to increase free radical production by ISO. Administration of LSFJ showed a significant improvement in serum uric acid level and serum protein levels as compared to ISO and CCl_4 injected rats. Similar results were obtained by Upaganlawar and Balaraman (2010a) who showed that serum creatinine, blood urea nitrogen (BUN) and serum uric acid increased significantly, whereas serum total protein decreased in ISO group. Administration of LSFJ to ISO injected rats (LSFJ + ISO) showed a significant ($P \leq 0.05$) increase in the total protein level LSFJ administered rats showed decrease in uric acid level compared to ISO injected rats. Mahurkar *et al.,* (2012) reported the treatment with the aqueous and LSFS serum creatinine, blood urea nitrogen (BUN) and serum uric acid significantly decreased whereas serum total protein increased as compared with toxic control group. A significant improvement in kidney function at $P \leq 0.05$ level in urea and uric acid was found. Liver function markers showed significant reduction at $P \leq 0.001$ level in bilirubin levels.

Table (2): Effect of feeding *lagenaria-siceraria* juice on catalase, GPx, total protein (TP) and uric acid (UA) of rats

Groups	GPx (ng/mL)	Catalase (Mmol/L)	T.P(mg/dl)	U.A(mg/dl)
Control	32.886 ^{b}±5.17	57.45 ^{ab}±2.34	6.16^{b}±0.13	1.406 ^{d} ±0.172
Yaqtin	39.99 ^{a}±0.125	62.66 ^{a}±1.42	6. 65^{a}±0.185	1.23 ^{d} ±0.026
CCl_4	10.21 ^{d}±3.36	16.5 ^{e}±3.15	3.42 ^{d}±0.085	3.203 ^{a}±0.081
Tr+ CCl_4	17.17 ^{c}±2.53	29.66 ^{cd}±2.03	5.39^{c}±0.00	2.433 ^{b}±0.282
Pro+ CCl_4	28.76 ^{b}±1.058	33.16 ^{c}±1.75	5.51^{c}±0.205	1.813 ^{c}±0.0585
Iso	19.06 ^{c}±0.138	22.66 ^{de}±3.77	3.05^{d}±0.145	3.20 ^{a}±0.081
Tr+Iso	29.126 ^{b}±0.27	52.26 ^{b}±0.38	5.42^{c}±0.335	2.44 b±0.270
LSD	4.500	9.4318	0.347	0.2512

Means in the same column with different litters are significantly different at ($p \leq 0.05$).

3. Effect of feeding *lagenaria siceraria* juice on liver functions and kidney functions of rats

Table (3) revealed the mean value of GOT (U/L) of tested rats group. It could be noticed that the mean value of GOT (U/L) of CCl_4 and ISO groups were higher than negative control group and Yaqtin group, which showing significant changes increased between positive groups with CCl_4 or ISO and both control group and Yaqtin group. Administration orally LSFJ had protective and treatment against CCl_4 and ISO which revealed significant decreases in mean value as compared to toxic groups CCl_4 and ISO. There is no significant differences between CCl_4 group and ISO group also, there is no siginificant between negative control group, Yaqtin group and Tr + ISO. The best GOT (U/L) was recorded for group (Tr+Iso).

Concering the mean value of GPT (U/L), the mean value of GPT(U/L) of toxic groups with CCl_4 and ISO which being 70.0 ± 18.68 and 67.33 ± 11.13 U/L respectively. Rats administered orally LSFJ as protective or treatment (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) which revealed significant decreases in mean value as compared to positive control groups with CCl_4 and ISO. The values were 58.33 ± 4.72, 43 ± 8.88 and 48.66 ± 4.58 U/L respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. Rats on CCl_4 group and ISO group showed no significant differences between them. The best GPT (U/L) was record for group (Tr+Iso) when compare with negative control.

For the mean value of ALP (U/L), It could be noticed that the mean value of ALP (U/L) of toxic groups with CCl_4 and ISO were higher than negative control group and Yaqtin group, being 622 ±17.5, 555.33 ±19.28, 245.66 ±6.42 and 259.33 ±6.61 U/L respectively, showing significant difference increased of toxic groups CCl_4 and ISO as compared to control group and Yaqtin group. Rats administered orally LSFJ protective or treatment (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) revealed significant decreases in mean value as compared to toxic groups CCl_4 and ISO. The values were 421.33±33.23, 378.33 ± 19.7 and 275 ± 10.44 U/L respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. Rats on CCl_4 group and ISO group showed no significant differences between them. Rats on Pro+ CCl_4 group and Tr + CCl_4 showed no significant differences between them. The best ALP (U/L) was record for group (Tr+Iso).

Also, it could be noticed that the mean value of creatinine and uear (mg/100ml) of positive control groups with CCl_4 or ISO was higher than negative control group and Yaqtin group, this increasing being significant. Rats administered orally LSFJ protective or treatment (Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO) revealed significant decreases in mean value as compared to positive control groups CCl_4 and ISO. There is a significant change between rats fed on Pro+ CCl_4 group and Tr + ISO for creatinine and urea. The best creatinine and urea mean value (mg/100ml) were recorded for group (Tr+ISO) when compare with negative control.

These result are in agreement with Shirwaikar and Sreenivasan (1996) who reported that a hepatoprotective activity was assessed by examining the influence of the ethanolic extract of *Lagenaria siceraria* (EELS) (in doses 100 and 200 mg/kg) on hepatotoxicity induced by administration of CCl_4. Administration of the ethanolic extract of *Legenaria siceraria* fruit (EELS) orally to different groups of rats reduced the level of SGOT, SGPT, ALP, ACP enzymes, all fractions were tested, in a dose of 250 mg/kg showed significant activity. *Lagenaria siceraria* (bottle gourd) was reported to have several health benefits .Liver function markers showed significant reduction at $P \leq 0.001$ level in bilirubin levels (Katare *et al..* 2012). Satyajeet *et al..* (2013) reported that groups that received EELS [100 mg/kg and 200 mg/kg], in combination with anti tubercular drugs, showed a significant reduction [p value ≤0.001] in biochemical parameters for hepatotoxicity [SGOT, SGPT, ALP, Total bilirubin, Total protein]

Also, Katare *et al..* (2012) found a significant improvement in kidney function at $P \leq 0.05$ level in urea and uric acid was found and liver function markers showed significant reduction at $P < 0.001$ level in bilirubin levels.

Table (3): Effect of feeding *lagenaria siceraria* juice on liver function and kidney functions of rats

Parameter / Groups	GOT (U/L)	GPT(U/L)	ALP(U/L)	Creatinine (mg/100ml)	Urea (mg/100ml)
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Control	56.33 ^{e}± 3.21	36 ^{c} ± 3.60	245.66 ^{c}±6.42	0.88^{cd} ± 0.091	29^{b} ± 1.02
Yaqtin	55.00 ^{e}± 3	37.66 ^{c} ± 3.76	259.33 ^{c}±6.61	0.85 ^{de} ± 0.01	28^{bc}± 1.00
CCl4	114.66 ^{a} ± 6.42	70.0 ^{a} ± 18.68	622 ^{a} ±97.5	1.206^{a} ± 0.09	33^{a} ± 1.11
Tr+ CCl4	84.33 ^{c} ± 23.06	58.33 ^{ab} ± 4.72	421.33^{b}±33.23	0.95^{b} ± 0.01	27 ^{c} ± 1.2
Pro+ CCl4	73.33 ^{d}± 7.02	43 ^{bc} ± 8.88	378.33 ^{b}± 19.7	0.79 ^{e}± 0.02	25.66^{d} ± 2.0
Iso	97.33 ^{b}± 4.16	67.33 ^{a} ± 11.13	555.33 ^{a}±29.28	1.01^{bc} ± 0.026	33^{a} ± 1.0
Tr+Iso	58.66 ^{e} ± 7.02	48.66 ^{bc} ± 4.58	275 ^{c}± 10.44	0.76^{e} ± 0.02	27^{c} ± 0.01
LSD	8.935	15.23	74.601	0.0835	1.164

Means in the same column with different litters are significantly different (P ≤0.05).

4. Effect of feeding with *Lagenaria siceraria* juice on lipid fraction of rats.

Table (4) illustrates the mean value of total cholesterol (mg/dL) of rats feeding on LSGJ. It could be noticed that the highest mean value of total cholesterol (mg/dL) was for positive control groups of CCl_4 and ISO which was being 87.33 ±2.08 and 92.33±2.52 respectively while, the lowest mean value was detected in negative control group and Yaqtin groups (76±4.36 and 56.33±7.37 mg/dL respectively). The values were 73.33 ±3.51, 69.66 ±0.57and 75 ±1.00 mg/dL respectively for Tr+ CCl_4, Pro+ CCl_4 and Tr+ISO. There were significant changes between both of controls and the other tested groups.

In the same table, it could be observed for the mean values of triglycerides, HDL-C and LDL (mg/dL) of rats feeding LSGJ with toxic chemicals with CCl_4 and ISO. There are no significant differences between both positive controls while there were significant changes between positive control groups and the tested groups which fed on Yaqtin as protective and treatment. The best mean values of triglycerides, HDL-c and LDL-c (mg/dL) were recorded for group Yaqtin then (Tr+ISO).

These results correlate with previous studies which have demonstrated the involvement of oxidative stress. *Lagenaria siceraria* is rich in cardiac glycosides, alkaloids, saponins, tannins, and flavonoids. Alkaloids usually have marked physiological action on animals. Saponins on the other hand are of great pharmaceutical importance because of their relationship to compounds such as the sex hormones, cortisones, diuretic steroids, vitamin D and cardiac glycosides (Evans, 2002; Olajide *et al.*, 2004; Nainwal *et al*.,2011 and Rajput *et al*., 2014).

Katzung, (2004); Ghule *et al*., (2006b); Mohale *et al.,* (2008) and Ghule *et al.* (2010) reported oral administration of the extracts dose dependently inhibited the total cholesterol, triglycerides, low-density lipoproteins level, and significantly increased the high-density lipoproteins level.

Table (4): Effect of feeding with *Lagenaria siceraria* juice on lipid fraction of rats

Parameter/ Groups	Lipid Fraction		HDL-C (mg/dL) Mean±SD	LDL(mg/dL)
	Total cholesterol (mg/dL) Mean ± SD	Triglycerides(mg/dL)		
Control	76 ^{b}±4.36	77 ^{d} ±2.645	31.33^{bc}±1.52	26.66^{bc}±2.08
Yaqtin	56.33^{c}±7.37	81 ^{cb}±4.58	34.33^{a}±2.88	13 ^{e}±2.64
CCl_4	87.33 ^{a} ±2.08	96.33 ^{a} ±2.88	28 ^{d} ±1.0	31.33^{a}±1.53
Tr+ CCl_4	73.33 ^{b}±3.51	85.33 ^{bc} ±2.52	30.66 ^{bc} ±1.0	25.0 ^{c}±1.01
Pro+ CCl_4	69.66 ^{b}±0.57	83 ^{bc} ±1.0	32.33^{ab} ±2.08	21.66^{d}±1.53
Iso	92.33 ^{a} ±2.52	92.33 ^{a} ±2.51	29.3 ^{cd} ±1.12	29.0^{ab}±1.0
Tr+Iso	75 ^{b}±1.00	87 ^{b} ±1.0	32.66 ^{ab} ±1.0	24.0^{cd}±1.0
LSD	6.75	4.825	2.44	3.0894

Means in the same column with different litters are significantly different (P ≤0.05).

Vijayakumar *et al.,* (2010) administered rats, LDL and VLDL fractions were significantly increased with a decrease in HDL cholesterol in serum. Oral administration of EELSF (125, 250 and 500 mg/kg body weight) significantly reverted the levels of almost all the selected parameters to near normal . Nainwal *et al.* (2011) was undertaken to assess body weight, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and very low density lipoprotein (VLDL) were significantly lower in the juice extract treated groups compared to the control group; showed that juice of the fresh fruits of *Lagenaria siceraria* have the potential to cause a blood cholesterol lowering effect. Kannojia *et al.* (2012) suggested that aqueous extract of *Lagenaria siceraria* has a beneficial effect in treating hyperlipidemia and may serve as a potential drug for prevention of hyperlipidemic atherosclerosis. Kaur *et al.* (2015) was observed that the combinatorial extract of Lagenaria siceraria fruit (200 mg kg-1), Trigonella foenum graecum extract (200 mg kg-1) significantly decreased (p<0.001) the levels of triglyceride (TG), Low Density Lipoproteins (LDL), cholesterol and showed an increase in High Density Lipoproteins (HDL) levels.

5. DNA damage

Fig. (1) and Table (5) showed the effect of infection CCl_4 & Isoproterenol on DNA of rat's heart and treatment with *lagenaria-siceraria* fruit juice. Lane(1) non infected control ;non infected treated with *lagenaria-siceraria* fruit juice(2), protected with *lagenaria-siceraria* fruit juice then infected with CCl_4 (3), infected with CCl_4 then treated with *lagenaria-siceraria* fruit juice(4), infected with CCl_4 (5, 6) , infected with Isoproterenol (7), protected with *lagenaria-siceraria* fruit juice then infected with Isoproterenol (8,9)and lane 10 showed 100 pb DNA ladder.

The optical density of DNA is shown in Fig. (2) of gel proanalyzer chart. Protection and Treatment with *Lagenaria siceraria* fruit juice for three weeks showed increase in the intensity of intact DNA when compared with infected controls with values 209.473, 197.372, 126.551, 104.527 and 93.747 at 800, 600,400 and 200pb, respectively.

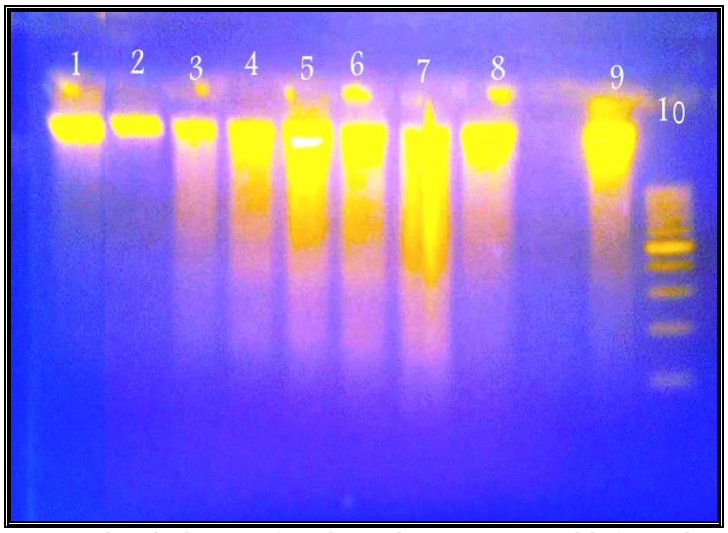

Fig. (1): DNA fragmentation in heart of CCl_4 and Isoproterenol infected rate post infection and treated with (Yaqtin) *Lagenaria siceraria* fruit juice:

Lane 1: Non infected control
Lane 2: Non infected treated with (Yaqtin) Lagenaria siceraria fruit juice
Lane 3: Infected protective with (Yaqtin) Lagenaria siceraria fruit juice
Lane 4: Infected treated with (Yaqtin) Lagenaria siceraria fruit juice
Lane 5, 6: Infected control with CCl_4
Lane 7: Infected control with ISO
Lane 8, 9: protective with Lagenaria siceraria fruit juice &Infected with ISO
Lane 10: 100 pb DNA ladder

Table (5): DNA fragmentation in heart of CCl_4 & Isoproterenol infected rate post infection and treated with (Yaqtin) *Lagenaria siceraria* fruit juice.

Lane	Lane No	intactDNA	Mean1	Mean2	Mean3	Mean4
			800pb	600pb	400pb	200pb
1	Ctrl	209.473	197.372	126.551	104.527	93.747
2	Yaqtin	183.748	173.517	128.412	111.136	94.876
3	Protected+ CCl_4	224.749	215.844	162.887	127.743	104.504
4	Treatment+ CCl_4	224.592	216.743	192.735	150.396	129.703
5	CCl_4	223.531	204.611	175.817	142.267	116.092
7	Iso	229.529	215.261	215.271	164.922	133.504
9	Protected+ ISO	218.408	211.386	169.612	137.88	118.069

On the other hand, the intensity of released DNA in liver of infected mice with CCl_4 showed increase with values 204.611, 175.817, 142.267, and116.092 at 800, 600,400 and 200pb, respectively; the intensity of released DNA in liver of infected mice with Isoproterenol showed increase with values also, 215.261, 215.271, 164.922

and 133.504 at 800, 600 ,400 and 200pb, respectively.

Administration of treatment with *Lagenaria siceraria* fruit juice increased the intensity of released DNA show apoptotic bands at 200, 400, 600, and 800 pb with values 104.56, 119.104, 135.692, 159.604, respectively. As well as, protective rats for 3 weeks and treated with *Lagenaria siceraria* fruit juice show increase in intact and decrease in released DNA at 200,400,600 and pb with values 108.006, 131.276, 153.588 and 192.544 respectively. This result proved prevention better than treatment.

Fig. (2) and Table (6) showed the effect of infection CCl4 & Isoproterenol on DNA of rat's liver and treatment with *Lagenaria siceraria* fruit juice. Lane 11 showed 100 pb DNA ladder and lanes1, 2,3,4,5,6,7, 8,9,and 10 represented the groups non infected control (1,2);non infected treated with Lagenaria siceraria fruit juice(3), infected with CCl_4(4,6) , protected with Lagenaria siceraria fruit juice then infected with CCl_4 (5), infected with CCl_4 then treated with Lagenaria siceraria fruit juice(7), infected with Isoproterenol (8,9), protected with Lagenaria siceraria fruit juice then infected with Isoproterenol (10).

The optical density of DNA is shown in Fig. (2) Of gel proanalyzer chart. Protection & Treatment with Lagenaria siceraria fruit juice for three weeks showed increase in the intensity of intact DNA when compared with infected controls with values 229.781, 117.36, 81.513, 70.863 and 60.816 at 800, 600,400 and 200 pb, respectively.

The intensity of released DNA in liver of infected mice with CCl4 showed increase with values 170.766, 138.614, 122.508 and 109.307 at 800, 600,400 and 200pb, respectively; the intensity of released DNA in liver of infected mice with Isoproterenol showed increase with values also, 166.367, 152.298, 122.611and 113.449at 800, 600 ,400 and 200pb, respectively.

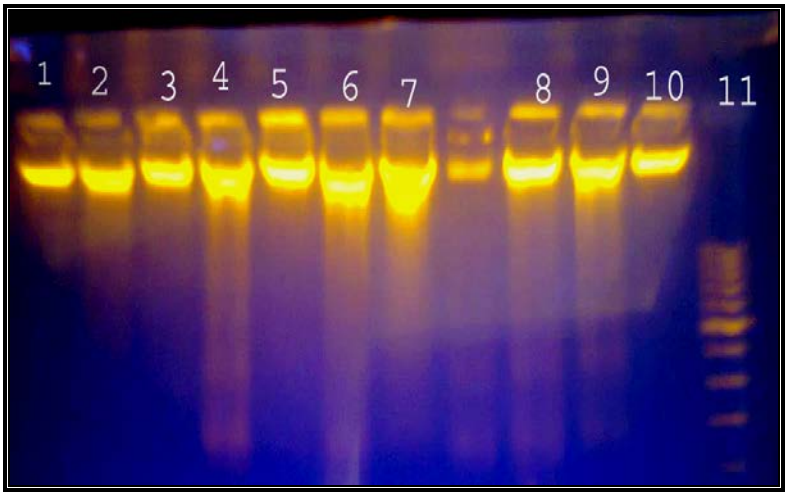

Fig. (2): DNA fragmentation in liver of CCl4 and Isoproterenol infected rate post infection and treated with (Yaqtin) *Lagenaria siceraria* fruit juice:

Lane 1, 2: Non infected control
Lane 3: Non infected treated with (Yaqtin) Lagenaria siceraria fruit juice
Lane 4: Infected control with CCl_4
Lane 5: Infected protective with (Yaqtin) Lagenaria siceraria fruit juice
Lane 6: Infected control with CCl_4
Lane 7: Infected treated with (Yaqtin) Lagenaria siceraria fruit juice
Lane 8, 9: Infected control with ISO
Lane 10: protective with Lagenaria siceraria fruit juice& infected with ISO
Lane 11: 100 pb DNA ladder

Table (6): DNA fragmentation in liver of CCl_4 & Isoproterenol infected rate post infection and treated with (Yaqtin) *Lagenaria siceraria* fruit juice.

lane	Groups	Intact DNA	Mean1	Mean2	Mean3	Mean4
			800pb	600pb	400pb	200pb
1	Ctrl	229.781	117.36	81.513	70.863	60.816
3	Yaqtin	248.564	150.483	116.512	99.843	80.064
4	CCl_4	240.543	170.766	138.614	122.508	109.307
5	Protected+ CCl_4	244.068	146.9	102.375	86.413	74.035
7	Treatment+ CCl_4	250.053	159.604	135.692	119.104	104.56
8	ISO	242.662	166.367	152.298	122.611	113.449
10	Protected+ ISO	253.581	144.114	107.475	102.335	88.97

Administration of treatment with Lagenaria siceraria fruit juice increased the intensity of released DNA show apoptotic bands at 200, 400, 600, and 800 pb with values 104.56, 119.104, 135.692, 159.604, respectively. As well as, protective rats for 3 weeks and treated with Lagenaria siceraria fruit juice show increase in intact and decrease in released DNA at 200,400,600 and pb with values 74.035, 86.413, 102.375 and 146.9, respectively. This result proved prevention better than treatment

These results are agreement with Tiwari *et al.,*(2014) indicated that juice of Ivy gourd (IG) fruit (Coccinia grandis L. J.Voigt) and Banana stem (BS, Musa paradisiaca L.),were most potent in preventing FR induced damage to DNA followed by Bottle gourd (BG) fruit (*Lagenaria siceraria* Molina standl).

In conclusion, the present study concluded that the protective effect of LSFJ on Ccl_4&ISO-induced in rats. These effects might be due to the presence of polyphenolic components in the fruit of LS. Further study is required with higher doses/duration of treatment with LSFJ to confirm its cardioprotective activity.

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التاثير الوقائى لليقطين من أمراض إحتشاء عضلة القلب الناتجة من ايزوبروتيرينول ورابع كلوريد الكربون في الفئران

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تهدف الدراسة إلى تقييم آثارعصير ثمرة اليقطين فى الوقاية من احتشاء عضلة القلب الناتجة من الاصابة برابع كلوريد الكربون (CCl_4) والايزوبروتيرينول .الفئران المحقونة بواسطة (ايزوبروتيرينول (٨٥مجم /كجم تحت الجلد)– من رابع كلوريد الكربون ،اظهرت انخفاض كبير فى البروتين الكلي، الكاتليز، جلوتاثيون بيروكسيديز و الليبوبروتين عالى الكثافة و أظهرت زيادة كبيرة في مستويات حمض اليوريك في الدم، الصوديوم، الكالسيوم، الكرياتينين، اليوريا، و الكوليسترول الكلي والدهون الثلاثية،LDL ، GOT، GPTو ALP و كذلك أظهرت المجموعات المصابة بايزوبروتيرينول و رابع كلوريد الكربون حدوث زيادة كبيرة من تفتيت الحمض النووي وموت الخلايا المبرمج .وأظهرت المجموعات المعالجة بعصير اليقطين (٣٠ مل/ كجم/ يوم/ صباحا) تأثير تحسن فى التحاليل البيوكيميائية، أظهرت تحسن ملحوظ في الحمض النووى والتغيرات النسيجية .هذه النتائج تشير إلى التأثيرات الواقية لعصير اليقطين على إحتشاء عضلة القلب في الفئران والتي يسببها رابع كلوريد الكربون , ايزوبروتيرينول .

الكلمات الاستهلالية: رابع كلوريد الكربون(CCl_4) ، ايزوبروتيرينول، اليقطين(قرع الزجاجة) ،احتشاء عضلة القلب