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Protective Effect of Lepidium Sativum Seeds and Captopril Against Cisplatin-Induced Hepato-Cardio Toxicity in Rats

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Abstract

Background: Cisplatin (Cis) is one of the most potent chemotherapeutic antitumor drugs. The therapeutic efficacy of Cis is limited by its severe side effects comprising kidneys heart and liver toxicity Lepidium sativum seeds (LSS) (family: Cruciferae) has been used in traditional medicine for the treatment of jaundice, liver problems, spleen diseases and gastrointestinal disorders.

Aim of Study: The aim of this study is to investigate the hepato-cardio protective effects of Lepidium sativum seedsextract. (LSSE) and/or Captopril (Cap) on Cis-intoxicated rats.

Material and Methods: Seventy adult male albino rats were used, they were fed rodent chow diet for 14 days (experimental period). Rats were categorized in 7 groups (10 rat/group). Group 1, normal control, intraperitoneally injected with 2ml saline solution at day 10 of experiment. Group 2, received a single intraperitoneal injection of 7.5mg/kg BW Cis at day 10 of experiment. Group 3, orally administered 60 mg/kg B.W captopril for 14 days with the same course of Cis-injection. Group 4 and 5 received oral administration of 200 and 400mg/kg B.W LSSE respectively along with the same course of Cis-injection. Group 6 and 7 received oral administration of 200 and 400 mg/kg B.W LSSE with 60mg Cap, along with the same course of Cis-injection.

Results: Cis-toxicity were evidenced by significant increase in malondialdehyde, MDA (as an index of lipid peroxidation) and in serum levels of hepatic enzymes and lactate dehydrogenase, LDH as well as in pro-inflammatory markers tumor necrosis factor α (TNF-α) and interlukin-6 (IL-6). However, the levels of glutathione (GSH) and Copper and zinc superoxide dismutase (Cu/Zn SOD) were decrease. Concurrent administration of LSSE and/or Cap attenuated-induced Cis-disturbances in liver and heart enzymes as Concurrent administration of well as oxidative status, and pro-inflammatory cytokine.

Conclusion: LSSE and Cap appear to be potent candidates to ameliorate hepatic and cardiac toxicity associated with Cis toxicity in rats.

Key Words: *Cisplatin – Lepidium sativum seed – Captopril – Rats – Glutathione – Maoldyaldehyde – Superoxide dismutase – Liver enzymes – Pro-inflammatory cytokines.*

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Introduction

CISPLATIN (cis-dichlorodiammine-platinum (II), Cis) is an inorganic platinum compound with a broad spectrum antineoplastic activity against various types of tumors, including cancers of the head, neck, esophagus, lung, bladder, ovary, cervix, breast, testis, penis, endometrium, mesothelium and many more **[1]**. The cytotoxic effect of cisplatin is believed to result mainly from its interaction with DNA, via the formation of covalent adducts between certain DNA bases and the platinum compound **[2]**.

Despite its effectiveness, the use of cisplatin in high-dose therapy has been reported to be limited by renal and cardiac toxicities **[3]**. Other side effects including, nausea, vomiting, myelosuppression, sensitivity reactions, at high-doses the drug is highly taken up in human liver and can alter the clinical situation of the patient **[4]**.

Angiotensin II, the central product of the renin–angiotensin–aldosterone system, induces tissue oxidative stress, inflammation and apoptosis **[5]**. Cap, an angiotensin-converting enzyme inhibitor, decreases the circulating and tissue levels of angiotensin II. Also, as a sulfhydryl (-SH) containing compound, captopril possesses powerful antioxidant activity, scavenges different types of reactive oxygen species and prevents lipid peroxidation **[5]**. It was reported that Cap protected against tissue injury induced by oxidative stress and inflammation in various experimental models **[6,7]**.

Dietary intervention using-plant based products, has long been considered a better strategy for either preventing or reducing the progression of chronic diseases. This is largely due to the affordability of these products along with fewer side effects they produce compared to the drugs administered under a pharmacological approach [8].

The World Health Organization (WHO) projected that 80% of the world's population relies on traditional medicines, and around 19.4 billion global revenues were recorded for herbal remedies in 2010. Moreover, the market demand for medicinal plants is increasing continuously and according to WHO the demand will be more than the US $ 5 trillion in 2050 [9].

Lepidium sativum (LS) popularly known as garden cress in different regions of the world is an edible annual and fast growing herb belongs to the family Brassicaceae [10]. Traditionally, LS is used for the treatment of various diseases like asthma, tumors of the uterus, ulcers, hemorrhoidal haemorrhage, coughing, wounds, dermatomycosis, dysmenorrhea, sciatica, and nasal polyps. The seeds of this species have been utilized as a galactagogues and abortive agent and are also used to treat sore throat, headache, cough, asthma, malaria, syphilis, and impotence. LS has been also reported to possess various biological activities such as antimicrobial, bronchodilator, hypotensive, allopathic, hypoglycemic, hepatoprotective, antioxidant [11]. The phytochemical profiling of LS showed the presence of flavonoids, phenols, cardiotonic glycosides, cardiac glycosides, alkaloids, coumarins, proteins, and amino acids [11].

The current study was designed to investigate the possible protective effect of LSSE and Cap on hepato- and cardio-toxicity induced by Cis in male albino rats.

Material and Methods

Material:

LSS were procured from a local market in Cairo, Egypt. The seeds were authenticated by Ministry of Agriculture, Land Reclamation, Agriculture Research Center, Horticultural Research Institute, Department of Flora Research and Plant Taxonomy. Seed specimen was deposited in the herbarium of the faculty of pharmacy Ain Shams University. Cap was purchased from Eipico pharmaceuticals, Cairo, Egypt. Cis was purchased from Mylan pharmaceuticals, Cairo, Egypt.

Methods:

Preparation of methanolic extract of LSS:

LSS were washed with double distilled water, de-shelled and dried and ground using pestle and mortar before extraction. The seeds were allowed to dry under the sunlight for two days. The seeds were then crushed and passed through a mesh #80 to get the fine powder and stored in dark containers free from moisture [12].

The seeds of LS were coarsely grinded and, macerated in distilled methanol for two weeks (kg seeds/3 liter methanol) in airtight large flask. The flask was filtered and maceration was repeated for two consecutive weeks. The combined filtrates were then evaporated under reduced pressure and dried using a rotary evaporator at 55°C, then it was lyophilized to give dry powder. The percentage yield of the extract was 7.33% [12].

Determination of nutritive value of LSS:

LSS was subjected to chemical analysis for the determination of its nutritive value. Macronutrients, some minerals and vitamins were measured. The contents of moisture, protein, ash, total carbohydrates and crude fiber were assayed as described by Association of Official Agricultural Chemists, AOAC [13], while fat concentration was determined as mentioned by Kasiramar et al. [14]. Moreover, Vitamin A and E were determined according to [15] using High-performance liquid chromatography instrument (HPLC), with column Agilent 1100, diode array Detector and quaternary pump while vitamin C was assayed as described by Serrano et al. [16] Mineral contents including, Ca, P, Na, K and Fe were determined in LSSE according to AOAC [17].

Biological experiment:

Ethics Committee approval:

This study was approved by the Research Ethics Committee (REC) at National Hepatology & Tropic Medicine Research Institute (NHTMRI), Cairo, Egypt. Serial number, A-4 2024.

Experimental animals:

Seventy adult male Sprague Dawley albino rats (weighing 150±10g) were purchased from the farm of the National Institute of Vaccination, Hellwan. Cairo, Egypt. They were individually housed in metallic cages under constant healthy environmental conditions, inexperimental animal unit of National Nutrition Institute, Cairo, Egypt. From 16 June to 6 July (2024).

Experimental diet:

Standard laboratory rodent chow and tap water were provided ad-libitum. The animals were acclimatized for a period of one week prior to the commencement of the experiment.

Preparation of Cap:

Cap was dissolved in saline solution and, administered to rats by oral gavage at a dose of 60mg/kg B.W/day for 14 days (experimental period).

Preparation of Cis:

Cis was prepared in saline solution, it was injected intraperitoneally in day 10 of the experiment as a single dose of 7.5mg/kg BW according to the study of Atessahin et al. **[18].**

Experimental design:

Rats were divided into seven groups (10 rats/ group):

- Group 1: (Negative control group), fed on the rodent chow diet for 14 days (experimental period). At day 10 they were injected intraperitoneally with 2ml saline solution.
- Group 2: (Positive control group), fed on the rodent chow diet for 14 days. At day 10 of the experiment, they received a single intraperitoneal injection of Cis 7.5mg/kg.
- Group 3: Fed on the rodent chow diet for 14 days together with oral administration of 60 mg/kg B.W Cap. They also received the same course of Cis- injection.
- Group 4 and group 5: Received the rodent chow diet for 14 days together with oral administration of 200 and 400mg/kg B.W of LSSE respectively. At day 10 of the experiment, the rats received the same course of Cis- injection.
- Group 6 and group 7: Fed on the rodent chow diet for 14 days with oral administration of 200 and 400mg/kg B.W of LSSEalong with oral administration of 60mg/kg B.W Cap. At day 10 of the experiment, the rats received the same course of Cis- injection.

Body weight gain and organs weights:

Body weight of rats was recorded at the beginning and end of experiment (14 days). After sacrificing of rats hearts and livers were immediately removed and weighed then the organs weight ratio was calculated. The relative weight of organs (%) was calculated as g/100 g body weight.

Blood sampling and tissue preparation:

At the end of the experimental period (14 days) rats were fasted for 12 hours before sacrifice, and they were anesthetized with diethyl ether. Blood samples were collected. Fresh blood samples and erythrocytes were kept for further analysis.

Immediately after sacrificing of rats, livers and hearts were isolated, plotted free from adhering blood, washed with cold saline, dried between filter papers and weighed. Ten percent liver homogenate was prepared in 10ml 1.15M potassium chloride (KCl) solution. The homogenate was used for estimation of hepatic MDA Another 10% of liver and heart homogenateswere prepared in cold water and used for hepatic GSH as well as hepatic and cardiac proinflammatory cytokines estimations.

Determination of biochemical parameters:

Determination of oxidative stress biomarkers:

GSH was determined in blood and liver homogenate as described by Beutler et al. **[19].** Serum and hepatic MDA were also investigated **[20].** Erythrocyte Cu/Zn SOD was estimated according to Kakkar et al. **[21].**

Dtermination of serum hepatic enzymes and LDH:

Serum liver enzymes including alanine aminotransferase (ALA) & aspartate aminotransferase (AST) Henry et al., **[22]** and alkaline phosphatase (ALP) **[23]** were measured. Cardiac enzyme, LDH **[24]** were also estimated.

Determination of pro-inflammatory markers in hepatic and cardiac tissue homogenates:

Liver and heart homogenates were used for the determination of TNF-α and IL-6. The tow cytokines were assayed using the Assay Max Mouse TNF-α and IL-6 ELISA kit purchased from Assay Designs Inc. (Ann Arbor, MI, USA), via a quantitative sandwich enzyme immunoassay according to the manufacturer protocol. The resultant color was evaluated by reading ELISA plates using an ELISA reader. The procedure of the used kit was performed according to the manufacturer's instructions.

Histopathological examination:

Suitable section of cardiac and hepatic tissues was fixed in 10% buffered formal saline and processed for preparation of 5 mm-thick paraffin sections. These sections were sequentially stained with haemtoxlin (HX) and eosin and sections were examined under the light microscope Culling, **[25].**

Statistical analysis:

Data were analyzed by SPSS statistical package version 17. Excel computer program was used to tabulate the results, and represent it graphically. Independent *t*-test was used to declare the significant difference between each two groups at $p<0.05$. Pearson correlation coefficient at $p<0.05$ was used to declare the significant correlation between the variables within each group (Stanford and Charles, 26).

Results

Nutritional value of LSS:

Nutritional value of LSS was determined, the following results 4.0; 25.5; 24.5; 4.2; 33.1 and 8.7 (g/100g DW), were obtained for moisture, fat, crude protein, ash, total carbohydrate and crude fiber respectively (Table 1). Moreover, LSS contained various values of elements. The highest content was detected for k (1100 mg%, while lowest one was for Fe (7.1% mg%). The levels of vitamins A, E and C of LSS were 214.7%, 199.1% and 5.6% respectively (Table 1).

Table (1): Nutritive value of LSS.

Type of nutrient	Nutrients	Concentration
Macronutrients	Moisture (gm%)	4.0
	Fat (gm%)	25.5
	Protein (gm/%)	24.5
	Ash (gm%)	4.2
	Total carbohydrate (gm%)	33.1
	Crude fiber (gm%)	8.7
Minerals	Calcium, Ca (mg%)	255
	Phosphorus, P (mg%)	556
	Potassium, K (mg%)	1100
	Sodium, Na (mg%)	15.4
	Iron, Fe (mg%)	7.1
Vitamin	Vitamin A (mg%)	214
	Vitamin E (mg%)	199.1
	Vitamin C (mg%)	5.6

%: Per 100 gm.

Effect of LSSE and/or Cap on body weight change and absolute and relative liver and heart weights of Cis-treated rats.

Data presented:

In Table (2), showed that in Cis-intoxicated rats, body weight change was significantly decreased (54.35%) as compared with normal control, while absolute and relative weights of liver (39.32%, 27.03% respectively) and heart (19.23%, 9.38% respectively) were significantly decreased. Pretreatment of Cap and LSSE induces significant elevation in body weight change except for group (5) that fed 400mg LSSE with Cis-injection. Additionally, absolute and relative organs weights were decreased in all groups as compared to positive control. The highest decrease was detected in rats that was given 400mg LSSE with 60mg Cap.

Effect of LSSE and/or Cap on oxidative stress biomarkers on Cis-treated rats:

Cisplatin injection caused significant increases serum and hepatic MDA levels, whereas it resulted in a decline in blood and hepatic GSH content along with erythrocyte Cu/ZnSOD, activity as shown in Table (3). However, Cap administration significantly amended this alteration. The best results were observed for blood GSH erythrocyte Cu/ZnSOD and serum MDA. Moreover, pre-administration of LSSE significantly ameliorated these effects in all treated groups. The highest amelioration was detected in group 7 rats that received 400mg of LSSE & 60mg of Cap and the lowest one was in group 4 that administered 200mg LSSE.

Table (2): Effect of LSSE and/or Cap administration on body weight gain, liver and heart weights of Cis-intoxicated rats* (Means ± SD).

Parameters	Experimental groups						
	Negative control	Cis-intoxicated group	Cap 60 mg + Cis.	200 mg LSSE extract + Cis	400 mg LSSE extract + Cis.	200 mg LSSE extract + 60 mg Cap + Cis	400 mg LSSE extract + 60 mg Cap + Cis
Body weight change (gm/ 2 weeks)	11.50±3.92	5.25±4.26a	8.50±5.08b	6.50±6.02b e	8.25±4.26	7.75±6.61b	9.00 ±1.60b
% Change	–	–54.35	61.9	23.81	57.14	47.62	71.43
Liver:							
Absolute weight (g)	5.34±0.34	7.44±0.79a	5.46±1.00b f	6.82±0.71g	5.81±0.69b,g	5.91±1.72g	5.22±1.00b
% Change	–	39.32	–26.61	–8.33	–21.91	–20.56	–29.84
Relative weight	3.33±0.40	4.23±0.41a	3.70±0.37b d	4.00±0.95f g	3.76±0.50b	3.42±0.47b	3.42±0.86
% Change	–	27.03	–12.53	–5.44	–11.11	–19.15	–19.15
Heart:							
Absolute weight (g)	0.52±0.079	0.62±0.07a	0.55±0.06b g	0.60±0.07d f g	0.54±0.06f	0.52±0.02b	0.44±0.05
% Change	–	19.23	–11.29	–3.23	–12.90	–16.13	–29.03
Relative weight	0.32±0.011	0.35±0.05a	0.29±0.01b	0.31±0.02b g	0.33±0.05g,	0.32±0.02b g	0.28±0.03b
% Change	–	9.38	–17.14	–11.43	–5.71	–8.57	–20.00

a: Significant difference from negative control group.

b: Significant difference from positive control group (administered Cis as a single dose of 7.5mg/kg B.W day 10 of experiment)

c: Significant difference from Cap (administered by oral gavage of 60 mg/kg B.W/day along with the same course of Cis- injection).

d: Significant difference from lower dose of LSSE (oral administration of 200 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).

e: Significant difference from higher dose of L.SSE (oral administration of 400 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).

f-Significant difference from lower dose of LSSE + Cap (oral administration of 200 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W /day along with the same course of Cis- injection).

g: Significant difference from higher dose of LSSE + Cap (oral administration of 400 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W/day along with the same course of Cis- injection). $p<0.05$. (10 rats/group). ☾: for 14 days).

Cis: Cisplatn. LSSE: Lipidum Sativum seed extract. Cap: Captopril. B.W: Body weight. SD: Standard deviation.

Table (3): Effect of LSSE and/or Cap administration on oxidative biomarkers of Cis. -intoxicated rats* (Means ± SD).

Parameters	Experimental groups						
	Negative control	Cis-intoxicated group	Cap 60 mg + Cis.	200 mg LSSE extract + Cis	400 mg LSSE extract + Cis.	200 mg LSSE extract + 60 mg Cap + Cis	400 mg LSSE extract + 60 mg Cap + Cis
MDA:							
Serum (nmol/ml)	0.67±0.21	1.18±0.11[a]	0.87±0.20[b,d,e]	0.95±0.20[b]	1.02±0.19[b,g]	0.89±0.13[b]	0.79±0.31[b]
% Change	–	76.12	26.27	19.49	13.56	24.57	33.05
Hepatic (nmol/g)	56.83±13.44	82.15±16.37[a]	61.84±10.88[b]	62.78±16.96[b,e]	57.80±16.29[b]	62.43±11.99[b]	56.46±7.43[b]
% Change	–	44.55	24.72	23.58	29.64	24.00	31.27
GSH:							
Blood (mg/dl)	264.01±33.93	174.63±8.75[a]	229.73±34.49 b,d,e,f,g	211.92±45.93[b,g]	248.42±47.61[b,g]	267.22±22.0[b,g]	297.75±52.58[b]
% Change	–	33.85	31.55	21.35	42.26	53.02	71.05
Hepatic (mg/g)	39.41±9.19	17.63±2.21[a]	35.26±13.11[b,g]	36.65±12.07[b,f]	41.49±11.57[b]	49.09±16.07 b	44.26±16.69[b]
% Change	–	55.27	17.63	107.88	135.33	178.45	151.05
Erythrocyte Cu/Zn SOD (unit/ml)	142.65±28.90	106.63±16.71[a]	139.77±17.24[b,f]	145.53±16.04[b,f]	149.86±23.19[b]	161.38±16.71 b	159.94±14.75[b]
% Change	–	25.25	31.08	36.48	40.54	51.35	50.00

a: Significant difference from negative control group.

b: Significant difference from positive control group (administered Cis as a single dose of 7.5mg/kg B.W day 10 of experiment)

c: Significant difference from Cap (administered by oral gavage of 60 mg/kg B.W/day along with the same course of Cis- injection).

d: Significant difference from lower dose of LSSE (oral administration of 200 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).

e: Significant difference from higher dose of L.SSE (oral administration of 400 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).

f-Significant difference from lower dose of LSSE + Cap (oral administration of 200 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W /day along with the same course of Cis- injection).

g: Significant difference from higher dose of LSSE + Cap (oral administration of 400 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W/day along with the same course of Cis- injection). $p<0.05$. (10 rats/group). : for 14 days). Seed extract.

Cis: Cisplatn. Cap: Captopril. LSSE: Lipidum Sativum seed extract. B.W: Body weight. SD: Standard deviation.

MDA: Maloaldehyde. GSH: Glutathione. Cu/Zn SOD: Coper and Zinc superoxide dismutase.

Effect of LSSE and/or Cap on serum hepatic enzymes and LDH of Cis-treated rats:

The amount of ALT, AST, ALP, and LDH in different groups was reported in Table (4). Induction of liver and heart toxicity by Cis caused marked significant increase in serum activity of AST, ALT, ALP and LDH as compared to normal rats. The protective effect of pretreatment with Cap and LSSE were manifested by the significant reduction of all these enzymes. The best protection was observed in rats that was given higher dose of LSSE together with 60mg Cap.

Effect of LSSE and/or Cap on hepatic and cardicIL-6 and TNF-α of Cis-treated rats:

The effect of Cis- treatment on pro-inflammatory markers, IL-6 and TNF-α was presented in Table (5). Hepato (263.27%, 283.84%) and cardio (295.78%, 411.93%) levels of IL-6 and TNF-α exhibited a significant marked elevation in Cis exposed rats as in comparison with normal control. The administration of Cap and/or LSSE prior to Cis injection significantly downregulated the increased levels of both pro-inflammatory markers. The highest downregulation was reported for group 6, 7, who was given the lower and higher doses of LSSE with 60mg Cap.

Table (4): Effect of LSSE and/or Cap administration on Serum activity of liver enzymes, AST, ALT, ALP and LDH of Cis-intoxicated rats* (Means ± SD).

Parameters	Experimental groups						
	Negative control	Cis-intoxicated group	Cap 60 mg + Cis.	200 mg LSSE extract + Cis	400 mg LSSE extract + Cis.	200 mg LSSE extract + 60 mg Cap + Cis	400 mg LSSE extract + 60 mg Cap + Cis
Serum AST (IU/L)	41.48±16.69	73.75±4.92**a**	56.17±13.33**b,g**	63.92±13.62**b,f,g**	56.19±14.27**b,f,g**	52.50±8.89**b,g**	41.77±8.11**b**
% Change	–	77.80	23.84	13.33	23.81	28.81	43.36
Serum ALT (U/L)	71.25±5.67	108.75±9.41**a**	98.01±9.01**b,f,g**	98.83±10.56**b,f,g**	94.17±12.29**b,f,g**	84.67±11.73**b,g**	69.00±13.15**b**
% Change	–	52.63	9.88	9.12	13.41**b,g**	24.14	36.55
Serum ALP (U/L)	337.00±18.89	624.75±164.17**a**	468.00±100.26 **b,e,f,g**	441.00±173.75**b,e,g**	391.50±109.33	357.00±53.63**b**	311.87±66.97**b**
% Change	–	85.54	25.09	29.41	37.33	42.86	50.08
Serum LDH (U/L)	834.14±245.8	1599.38±149.5**a**	1463.25±129.5 **b,e,f,g**	1406.50±115.2**b,f,g**	1331.06±133.4**b,f,g**	1094.25±129.2**b,g**	886.00±170.5**b**
% Change	–	91.74	8.50	12.06	16.78	31.58	44.60

a: Significant difference from negative control group.
b: Significant difference from positive control group (administered Cis as a single dose of 7.5mg/kg B.W day 10 of experiment)
c: Significant difference from Cap (administered by oral gavage of 60 mg/kg B.W/day along with the same course of Cis- injection).
d: Significant difference from lower dose of LSSE (oral administration of 200 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).
e: Significant difference from higher dose of L.SSE (oral administration of 400 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).
f-Significant difference from lower dose of LSSE + Cap (oral administration of 200 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W /day along with the same course of Cis- injection).
g: Significant difference from higher dose of LSSE + Cap (oral administration of 400 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W/day along with the same course of Cis- injection). $p<0.05$. (10 rats/group). (*: for 14 days).
Cis: Cisplatn. LSSE: Lipidum Sativum seed extract. Cap: Captopril. B.W: Body weight. SD: Standard deviation.
AST: Alanine aminotransferase. AST: Aspartate aminotransferase. ALP: Alkaline phosphatase. LDH: Lactate dehydrogenase.

Table (5): Effect of LSSE and/or Cap administration on hepatic and cardiac tissue levels of pro-inflammatory markers, IL-6 and TNF-α in Cis- intoxicated rats* (Means ± SD).

Parameters	Experimental groups						
	Negative control	Cis-intoxicated group	Cap 60 mg + Cis.	200 mg LSSE extract + Cis	400 mg LSSE extract + Cis.	200 mg LSSE extract + 60 mg Cap + Cis	400 mg LSSE extract + 60 mg Cap + Cis
Liver:							
IL-6 (pg/ml)	38.63±9.89	140.33±17.09**a**	72.00±6.99**b,d,e,f,g**	80.73±6.34**b,e,f**	40.37±10.96**b,f,g**	58.85±21.3**b,g**	53.12±16.16**b**
% Change	–	263.27	–48.69	–42.47	–71.23	–58.06	–62.15
TNF-α (pg/ml)	37.95±3.93	150.20±15.43**a**	83.47±14.79**b,f**	87.75±7.62**b,f,g**	80.92±14.75**b,f**	70.20±7.40**b**	71.66±18.57**b**
% Change	–	295.78	–44.43	–41.58	–46.13	–53.26	–52.29
Heart:							
IL-6 (pg/ml)	32.00±3.67	122.83±4.88**a**	79.28±9.77**b,d,e,f,g**	71.80±10.32**b,e,f,g**	59.63±14.43**b**	57.25±16.68**b**	50.08±10.95**b**
% Change	–	283.84	–35.46	–41.55	–51.45	–52.39	–59.23
TNF-α (pg/ml)	19.95±1.78	102.13.±8.00**a**	54.68±15.71**b,f**	61.83±12.19**b,f,g**	43.30±13.02**b**	41.68±5.39**b**	47.52±18..55**b**
% Change	–	411.93	–46.46	–39.46	–57.60	–59.19	–53.47

a: Significant difference from negative control group.
b: Significant difference from positive control group (administered Cis as a single dose of 7.5mg/kg B.W day 10 of experiment)
c: Significant difference from Cap (administered by oral gavage of 60 mg/kg B.W/day along with the same course of Cis- injection).
d: Significant difference from lower dose of LSSE (oral administration of 200 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).
e: Significant difference from higher dose of L.SSE (oral administration of 400 mg/kg B.W L.S. seed extract, along with the same course of Cis- injection).
f-Significant difference from lower dose of LSSE + Cap (oral administration of 200 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W /day along with the same course of Cis- injection).
g: Significant difference from higher dose of LSSE + Cap (oral administration of 400 mg/kg B.W L.S. seed extract + oral gavage of 60 mg Cap/kg B.W/day along with the same course of Cis- injection). $p<0.05$. (10 rats/group). (*: for 14 days).
IL-6: Interleukin-6. TNF-α: Tumor necrosis factor alpha.

Histopatjological results:

In the current study, the histopathological changes in hepatic and cardiac tissue samples obtained from all treatment groups were evaluated.

Histopathological results of liver:

Histopathological examination of liver sections of control group showed average central veins surrounded by average hepatocytes arranged in single-cell cords with intervening blood sinusoids, and average portal tracts with average bile ducts and average portal veins (Photo 1). However, the liver of Cis-treated rats showed histopathologic changes in the form markedly dilated congested central veins with detached lining, hepatocytes showed hydropic change, scattered apoptosis and bi-nucleation, and portal tracts showed markedly dilated congested portal veins and average bile ducts (Photo 2).

The liver of Cis-intoxicated rats that administered Cap liver showed dilated congested central veins with dilated blood sinusoid and peri-venular inflammatory infiltrate, hepatocytes showed scattered apoptosis and intra-lobular inflammatory infiltrate, and portal tracts showed dilated congested portal veins and average bile ducts (Photo 3).

Histopathological results of liver

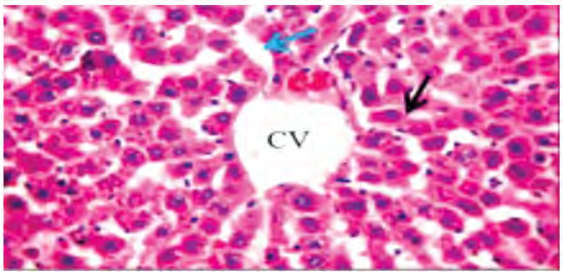

Photo (1): Photomicrograph of livers from normal control, high power view showing average central vein (CV) and average hepatocytes arranged in single-cell cords (black arrow) with average intervening blood sinusoids (blue arrow) (H&E X 400).

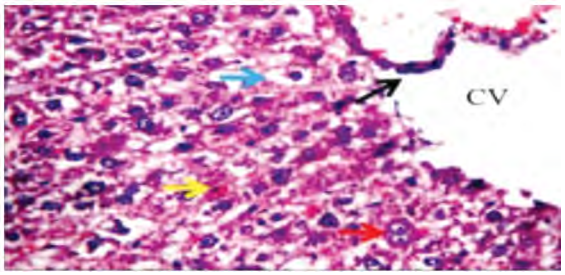

Photo (2): Photomicrograph of livers from cis-group high power view showing markedly dilated central vein (CV) with detached lining (black arrow), and hepatocytes showing hydropic change (blue arrow), scattered apoptosis (yellow arrow) and bi-nucleation (red arrow) (H&E X 400).

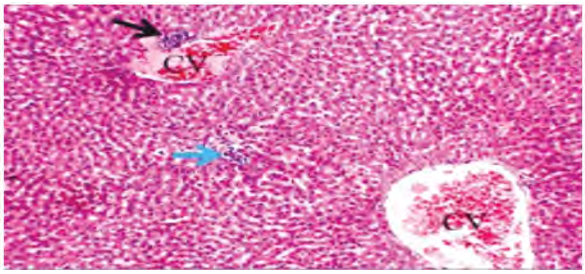

Photo (3): Photomicrograph of livers from cis + Cap liver showing dilated congested central vein (CV) with peri-venular (black arrow) and intra-lobular inflammatory infiltrate (blue arrow) (H&E X 200.

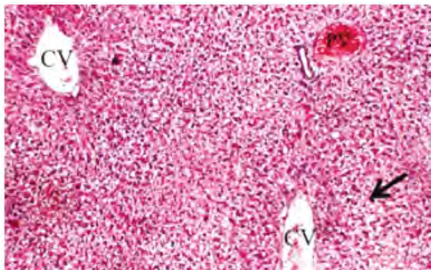

Photo (4): Photomicrograph of livers from cis + LSSE low dose: liver showing mildly dilated congested central vein (CV) and portal vein (PV), with mild hydropic change of hepatocytes (black arrow) (H&E X 200).

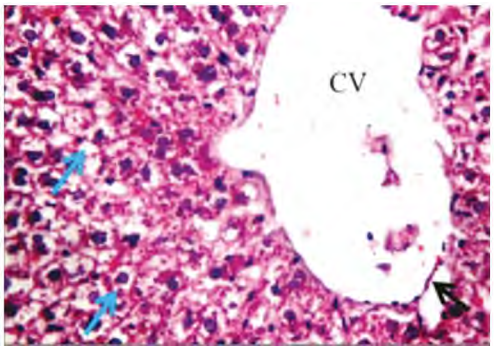

Photo (5): Photomicrograph of livers from cis + LSSE low dose: liver showing mildly dilated central vein (CV) with detached lining (black arrow) and mild hydropic change of hepatocytes (blue arrows) (H&E X 400).

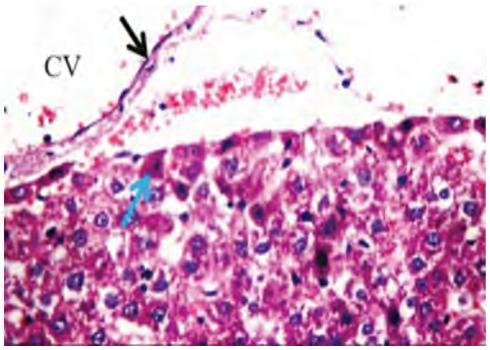

Photo (6): Photomicrograph of livers from cis + LSSE high dose: liver showing markedly dilated congested central vein (CV) with detached lining (black arrow), average hepatocytes (blue arrow), and average portal tract (red arrow) (H&E X 200).

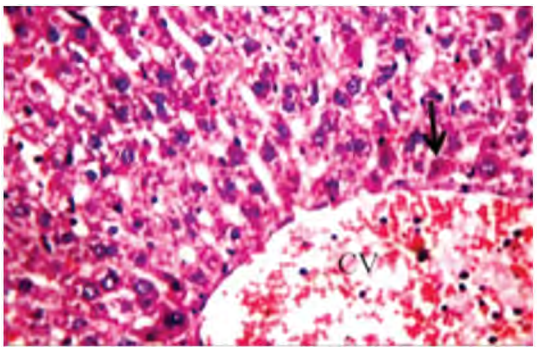

Photo (7): Photomicrograph of livers from cis + LSSE low dose + Cap: High power view showing markedly dilated congested central vein (CV) with scattered apoptotic hepatocytes inperi-venular area (black arrow) (H&E X 400).

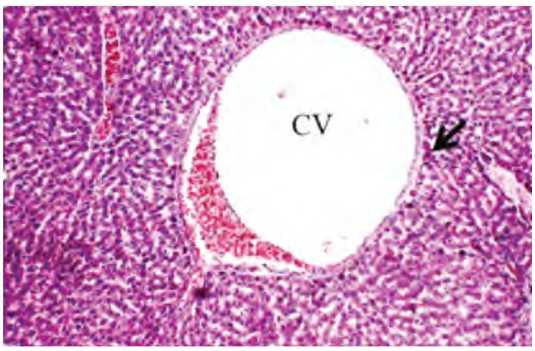

Photo (8): Photomicrograph of livers from cis + LSSE high dose + Cap: Liver showing markedly dilated congested central vein (CV), with apoptotic hepatocytes in peri-venular area (black arrow) (H&E X 200).

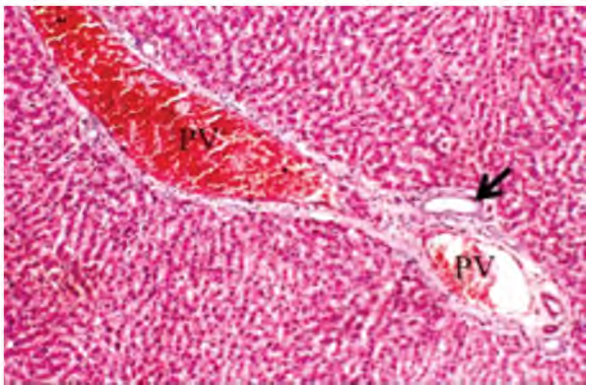

Photo (9): Photomicrograph of livers from cis + LSSE high dose + Cap: Another view showing portal tract with markedly dilated congested portal veins (PV) and average bile ducts (black arrow) (H&E X 200).

Regarding Cis-intoxicated rats that administered low dose of LSSE, liver tissues showed mildly dilated congested central veins with detached lining, hepatocytes showed mild hydropic change, and dilated congested portal veins (Photos 4,5), while histopathological results of group treated with high dose of LSSE was in the form of marked dilated congested central veins with detached lining, scattered apoptotic hepatocytes in peri-venular area, and portal tracts showed dilated congested portal veins and average bile ducts (Photo 6). Liver section of rats pre-treated with low dose of LSSE together 60mg Cap and the same Cis-injection showed markedly dilated congested central veins, scattered apoptotic hepatocytes in peri-venular area, and portal tracts showed markedly dilated congested portal veins and average bile ducts (Photo 7). Similarly, markedly dilated central veins, apoptotic hepatocytes in peri-venular area, and portal tracts showed markedly dilated congested portal veins and average bile ducts (Photos 8,9) were observed in group 7 that administered high dose of LSSE together with 60mg Cap and the same Cis-course.

Histopathological results of heart:

Heart section of rats from control group showed the following histopathological changes, average pericardium, average muscle fibers with average cell borders and average centrally located nuclei, and average blood vessels (Photo 10), while that of Cis-intoxicated rats were in form of pericardium, muscle fibers with indistinct cell borders and small pyknotic nuclei, and markedly dilated congested blood vessels (Photo 11). Heart section of rats pre-treated with Cap (Photos 12,13) showed average pericardium, muscle fibers with indistinct cell borders and small pyknotic nuclei, and markedly dilated congested blood vessels.

Histopathological picture of heart sections of Cis-rats treated with 200mg of LSSE revealed the presence of average pericardium, muscle fibers with indistinct cell borders and small pyknotic nuclei, and markedly dilated congested blood vessels (Photo 14). The heart sections from Cis-intoxicated rats that administered 400mg LSSE showed average pericardium, average muscle fibers with average cell borders and preserved cross striations, and mildly dilated blood vessels (Photo 15).

Moreover, average pericardium, muscle fibers with indistinct cell bordersand small pyknotic nuclei, and markedly dilated congested blood vessels (Photo 16) were observed in Ci-exposed rats treated with low dose of LSSE and 60mg Cap. Heart histology of group 7 that treated with 400mg LSSE beside 60mg Cap with the same Cis-course, showed average pericardium,muscle fibers with average cell borders and average nuclei, and mildly dilated congested blood vessels (Photos 17,18).

Histopathological results of heart

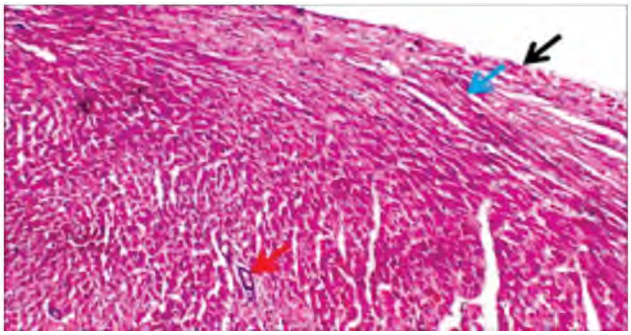

Photo (10): Photomicrograph of heart from normal control: Heart showing average pericardium (black arrow), average muscle fibers (blue arrow) with average blood vessels (red arrow) (H&E X 200.

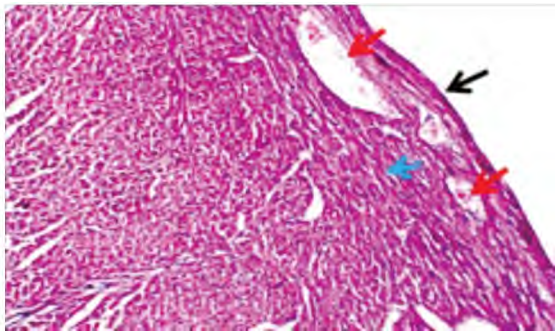

Photo (11): Photomicrograph of heart from Cis group: Heart showing average pericardium (black arrow), average muscle fibers (blue arrow) with markedly dilated congested blood vessels (red arrows) (H&E X 200).

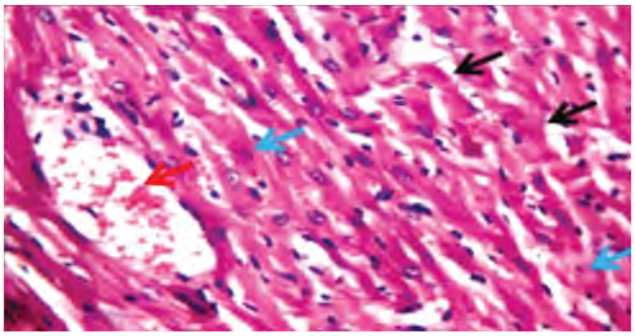

Photo (12): Photomicrograph of heart from Cis+Cap group: high power view showing muscle fibers with indistinct cell borders (black arrows) and small pyknotic nuclei (blue arrows), and markedly dilated congested blood vessels (red arrow) (H&E X 400).

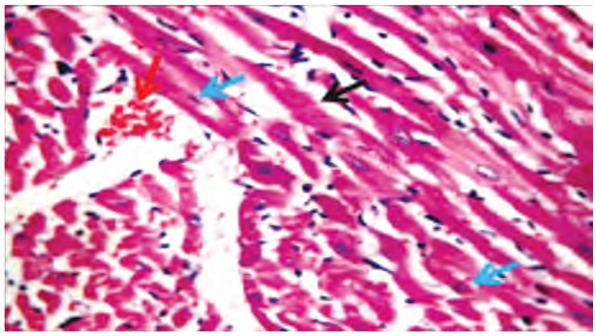

Photo (13): Photomicrograph of heart from Cis+Cap group: High power view showing muscle fibers with indistinct cell borders (black arrows) and small pyknotic nuclei (blue arrows), and markedly dilated congested blood vessels (red arrow) (H&E X 400).

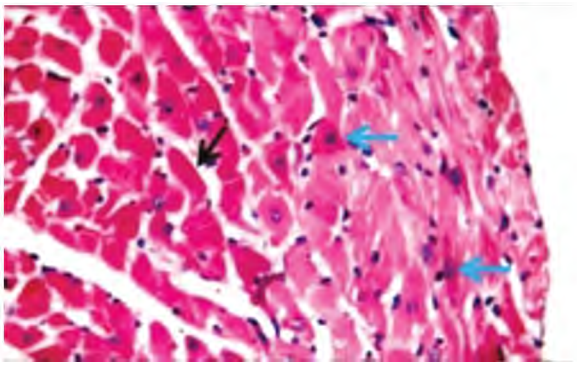

Photo (14): Photomicrograph of heart from Cis+ low dose group: High power view showing average muscle fibers with sdistinct cell borders (black arrows) and average nuclei (blue arrows) (H&E X 400).

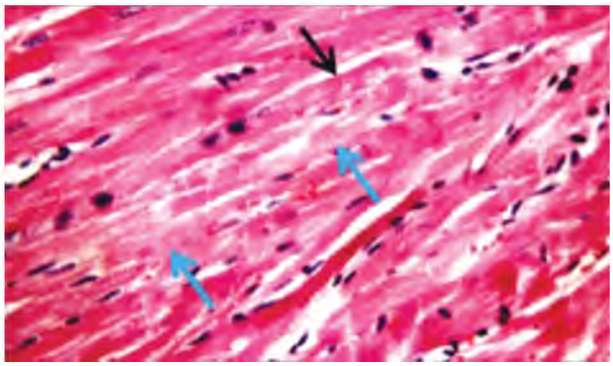

Photo (15): Photomicrograph of heart from Cis+ high dose group: High power view showing average muscle fibers with average cell borders (black arrows) and preserved cross striations (blue arrows) (H&E X 400).

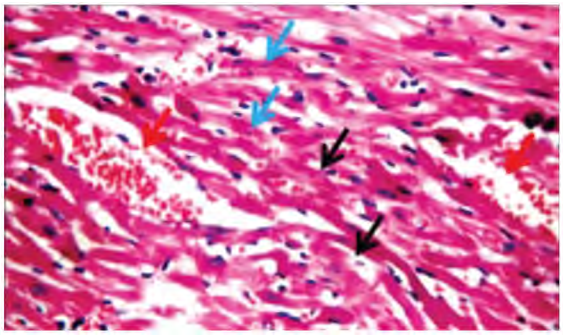

Photo (16): Photomicrograph of heart from Cis+ + Cap +low dose group: High power view showing muscle fibers with indistinct cell borders (black arrows) and small pyknotic nuclei (blue arrows), and markedly dilated congested blood vessels (red arrows) (H&E X 400).

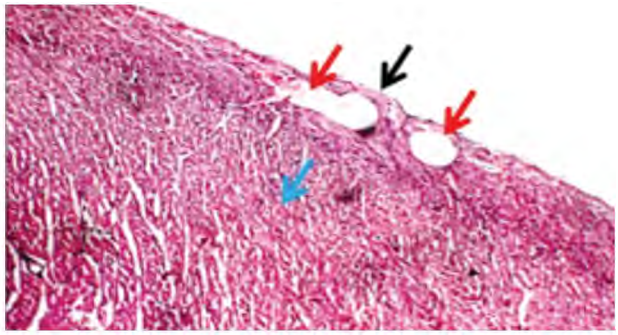

Photo (17): Photomicrograph of heart from Cis+ + Cap +high dose group: Heart showing average pericardium (black arrow), average muscle fibers (blue arrow), and mildly dilated blood vessels (red arrows) (H&E X 200).

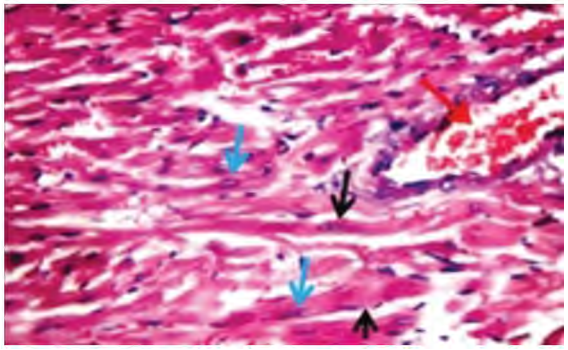

Photo (18): Photomicrograph of heart from Cis+ + Cap + high dose group: high power view showing muscle fibers with distinct cell borders (black arrows) and average nuclei (blue arrows), and mildly dilated congested blood vessels (red arrows) (H&E X 400).

Discussion

The nutritive value of LSS:

Results of the present study were in agreement with those of Doke and Guha **[27]**, they published that the chemical composition of LSS indicates the presence of high amounts of protein (22.47%-25.00%) and lipids (14.00%-28.03%) which indicated that seeds have high food energy, with low moisture content (3.92%-4.14%) which an index of stability quality and increased shelf life of seeds. They also detected the following ratios (6.75%-16.50%), (4.25%-4.65%) and (32.87%-54.00 %) for crude fiber, ash and carbohydrates respectively. However, Salem et al. **[28]** detected percentages of 7.05%, 4.8%, 18.79%, 19.73%, 35.45% and 14.18 for moisture, ash, crude fiber, protein, carbohydrates and fat respectively. The differences between this study and the present work may be attributed to geographic origin of the plants, growing conditions, and environmental factors.

The results given in Table (1) indicated that the nutritional activity in LSS is related to the particular vitamins, it contained good amounts of vitamins including, vitamin A, E, C and other vitamins. However, the results of Yadav et al. **[29]** were comparable to those of the present work. Moreover, Kadam et al. **[30]** published that total tocopherol content was 139.73±0.91mg/100g for LSS.

Body weight change, absolute and relative liver and heart weights:

Eid et al. **[31]** found that Cis administration to rats decreased body weight to 87.7% of control. This may confirm the present work. Moreover, a significant decrease in body weight after injection of Cis was also observed by Atessahin et al. **[32].** The weight loss of animals treated with cisplatin can be at least partially due to the drug toxicity which accelerates the water elimination in urine. Also, cisplatin-induced weight loss might be due to gastrointestinal toxicity and thereby reduced ingestion of food **[33].**

Oxidative stress biomarkers:

The present study, Cis injection markedly increased serum and hepatic MDA levels, whereas it resulted in a decline in blood and hepatic GSH content and erythrocyte Cu/ZnSOD activity as compared to the positive control group. Similar results were obtained for MDA, GSH and SOD in hepatic tissues **[34,35]** and in cardiac-tissues **[36].** These findings may support our results.

It has been suggested that oxidative stress is an important mechanism of cisplatin-induced toxicity possibly due to depletion of glutathione **[37].** The depletion of GSH seems to be a prime factor that permits lipid peroxidation **[38]**. In the present study, the observed decline in the level of GSH in cisplatin treated rat as compared to control group indicated that the depletion of GSH resulted in enhanced lipid peroxidation, and excessive lipid peroxidation caused increased GSH consumption **[39].**

GSH is a strong antioxidant that shields cells from the oxidative damages and fall in GSH pool can make cells venerable to oxidative stress **[39].**

In addition, GSH and CAT work simultaneously to counteract the oxidation of proteins, lipids and DNA by abolishing ROS [40].

The decrease in SOD activity could cause the initiation and propagation of lipid peroxidation in the cisplatin treated rats [41]. Cisplatin has been demonstrated to cause loss of copper and zinc in the kidneys [38]. The decreased SOD activity might be due to the loss of copper and zinc which are essential for the enzyme activity. The decreased SOD activity is insufficient to scavenge the superoxide anion produced during the normal metabolic process [38].

Fasihi et al. [34] investigated the effect of Cap on Cis-induced hepatotoxity in rats. They reported that concomitant treatment of Cap with Cis induced significant decrease in hepatic MDA and significant increase in both hepatic GSH and SOD. The results of the present study are in well accordance with these findings. Similar effects were observed by other authors [7,31,42].

Angiotensin II, the central product of the renin–angiotensin–aldosterone system, induces tissue oxidative stress, inflammation and apoptosis [43]. Cap, an angiotensin-converting enzyme inhibitor, decreases the circulating and tissue levels of angiotensin II. Also, as a thiol containing compound, Cap possesses powerful antioxidant activity, scavenges different types of reactive oxygen species and prevents lipid peroxidation [44,45]. Moreover, Cap was found to enhance the enzymatic activity of superoxide dismutase and selenium-dependent glutathione-peroxidase [46].

Raish et al. [47] investigated the hepatoprotective effect of ethanolic extract of LSS against D-galactosamine/lipopolysaccharide induced hepatotoxicity in rat. LSSE significantly induced significant reduction in thiobarbituric acid reactive substances (TBARS), and significant elevation in hepatic GSH and SOD. The present results were in agreement with these findings. Other authors also confirmed the antioxidant activity of LSSE [48,49,50].

The antioxidant effect of LSSE may be possibly due to the LSSE contains numerous active compounds particularly phenolic compounds, such as tocopherol, which is one of the most powerful antioxidants that acts to protect unsaturated fatty acids from oxidative stress damage. Vitamin A and essential fatty acids protect against oxidation, and work to prevent damage to various body tissues from the negative effect of free radicals [51] and then maintain a balance between the mechanisms that cause the production of free and that help to get rid of those toxic radicals.

Hepatic and cardiac enzymes:

The hepato and cardio-cellular damages caused by Cis were also evaluated (Table 4). Significant elevation in serum AST, ALT, ALP and LDH activities were detected in the Cis group, as compared to normal rats. Previous studies have reported that cisplatin increases serum transaminases and LDH [35,36], which may confirm our results.The ability of Cis to cause alterations in the activity of hepatic enzymes could be a secondary event following Cis-induced liver damage with the consequent leakage from hepatocytes [52]. It is known that Cis is significantly taken up in human liver and there is a suggestion that the drug accumulates in significant amounts in hepatic tissue particularly when injected in high-doses [53]. Generally, liver toxicity of Cis is characterized by mild to moderate elevation of serum transaminases

Creatine kinase (CK) and LDH enzyme activities are considered to be important measures of myocardial injuries [54]. During cisplatin induced cardiotoxicity, there is an alteration in lipid peroxidation of cardiac membrane together with an increased leakage of CK and LDH from cardiac myocytes. It has been reported that cisplatin is potent enough to generate ROS [55] that in turn alters the myocardial membrane structures, functions and integrity and as a consequence, there is a leakage of cardiac enzymes [56].

In the present study, rise in serum activities of AST, ALT, ALP and LDH that were induced Cis-injection was significantly abridged by per-administration with Cap. These findings were supported by that of Azizi-Malekabadi et al. [57]. Who observed that administration of Cap significantly decreased the activity of AST, ALT and ALP in rats treated with lipopolysaccharide. Similar results were also obtained [34,58].

The hepatoprotective effect of ethanolic extract of LSS against CCl4-induced hepatic injury was investigated by Al-Asmari et al. [59]. Their findings demonstrated that administration of the extract caused significant reduction in serum activity of ALT, ALP, and AST in rats [60] and in New Zealand rabbits [48]. Similar results were also obtained by Balgoon et al. [61] against aluminum-induced injury in liver of albino rat. These findings may confirm our results.

Moreover, the hepatic and cardio protective effects of aquatic extract of LSS on dexamethasone-intoxicated rats was demonstrated [62], serum ALP and LDH were markedly reduced in rats fed LSSE in comparison to dexamethasone group.

The liver protection of LSSE may be related to flavonoid and phenolic compounds. It mainly contains polyphenolic and flavonoid compounds, which are the most important antioxidants. It has been confirmed that the presence of phenolic compounds can improve hepatic markers in hepatotoxicity [63]. 5’6-dimethoxy-2’,3’-methylenedioxy-7-C-β-D-glucopyranosyl isoflavone (an isoflavone serum lipids profile, free radicals, and

improves hepatic function in hepatotoxicity with paracetamol [64].

Pro-inflammatory cytokine:

It was reported that Cis-administration to rats induced significant increase in serum TNF-α and IL-6 [36], and in heart mitochondrial tissue homogenate [65]. These results were in accordance with our results.

Increasing evidence indicates that Cisinduces a myriad of inflammatory cytokines and chemokines including translocation of the redox-sensitive transcription factor nuclear factor kappa B (NF-κB) from the cytosol to the nucleus, which leads to production of tumor necrosis factor alpha (TNF-α) in cardiomyocytes, a pro-inflammatory that is actively involved in Cis-induced inflammation [66,67].

The result of the present study confirmed the protective effect of Cap against Cis-induced inflammation in rats, as indicated by the increased levels of TNF-α and IL-6. Our results may be confirmed by other reports which showing that pretreatment with Cap attenuated the increased levels of TNF-α induced in testicular tissues of rats by Cis [31] and in renal tissues of diabetic rats [68].

Captopril exerts its anti-inflammatory effects through, reducing the blood and tissue levels of angiotensin II by inhibiting the angiotensin-converting enzyme, and blocking the activation of NF-κB signaling pathway which promotes the transcription of cytokines including TNF-α and IL-6 [68,69]. These actions highlight the potential anti-inflammatory ability of Cap as protective agents against toxins-induced damage in rats.

The anti-inflammatory effect of LSS alleviated the hepatic increased levels of TNF-α and IL-6 in high fat diet fed rats. Other authors reported significant reduction of the two cytokinesin vivo [47,70] and in vitro [71,72]. These findings were consistent with our results.

It was suggested that the anti-inflammatory activity of aqueous and alcoholic extracts of LSS could be due to phenolic and flavonoid compounds in these seeds that downregulate the increase levels of hepatic proi-nflammatory markers, including TNF-α and IL-6 [36]. It was also reported that LSS oil contained high levels of γ-tocopherol (87.74mg/100g) [73] and it is known that γ-tocopherol can prevent inducible Nitric oxide synthase in activated macrophages. Diwakar et al. [74] also proposed that the decrease in nitric oxide, NO production in peritoneal macrophages might be due to the presence of α- linolenic acid and γ-tocopherol in L. sativum seed oil [75].

Conclusion:

It can be concluded that Cap and LSSE exhibit potent protective effect on hepatic and cardiac toxicity induced by Cis in rats that could be partly contributed by their antioxidant and anti-inflammatory activities. The best potent effect was observed in highdose LSSE and 60mg Cap fed rats indicating synergistic effect of both protective substances. So, Cap and LSSE can be considered a candidate to protect against cardiotoxicity commonly encountered with Cis treatment.

Conflicts of interest to disclose.

Acknowledgments:

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التأثير الوقائى لبذور حب الرشادو الكبتوبريل ضد سمية الكبد والقلب الناجمة عن السيسبلاتين فى الجرزان

الخلفية: يعد السيسبلاتين أحد أقوى الأدوية الكيميائية المضادة للأورام و لكن اثاره الجانبية الشديدة والتى تشمل سمية الكلى والكبد والقلب تحد من الفاعلية العلاجية له. تستخدامبذور حب الرشاد فى الطب التقليدى لعلاج اليرقان ومشاكل الكبد وأمراض الطحال واضطرابات الجهاز الهضمى.

الهدف: الهدف من هذه الدراسة هو دراسة التأثيرات الوقائية لمستخلص بذور حب الرشاد والكابتوبريل على الجرزان المسممةبالسيسبلاتين.

المواد والطرق: تم تقسيم سبعين فئرا ابيضا بالغا الى سبع مجموعات (١٠ فئرا لكل مجموعة). تم اطعام كل الفئران الوجبة الطبيعية لمدة ١٤ يوما (مدة التجربة). المجموعة ١: المجموعة الضابطة الطبيعية: تم حقنها داخل الغشاء البريتونى ب ٢ مليميتر من محلول ملحى فى اليوم العاشر من التجربة.المجموعة ٢: تم حقنها بجرعة واحدة ٧,٥ مجم/كجم من وزن لجسم بالسيسبلاتين داخل الغشاء البريتونى في اليوم العاشر من التجربة. المجموعة ٣: تم اعطاؤها جرعة ٦٠ مجم كابتوبريل/كجم عن طريق الفم من وزن الجسم لمدة ١٤ يوما مع نفس الجرعة من السيسبلاتين. المجموعتان ٤ و ٥: تلقتا عن طريق الفم جرعة ٢٠٠ و٤٠٠ مجم/كجم من وزن الجسمعلى التوالى من مستخلص حبوب حب الرشادجنبًا إلى مع نفس الجرعة من السيسبلاتين. المجموعة ٦ و ٧: تلقتا عن طريق الفم جرعة ٢٠٠ و٤٠٠ مجم/كجم من وزن الجسممن مستخلص بذور حب الرشادمع ٦٠ مجم من كابتوبريل، جنبًا إلى جنب مع نفس جرعة السيسبلاتين.

النتائج: تم إثبات سمية السيسبلاتين من خلال زيادة كبيرة فى المالونديالدهيد (كمؤشر على أكسدة الدهون) وفى مستويات الإنزيمات الكبدية ولاكتاتديهيدروجينيز فى مصل الدم، وكذلك فى العلامات المؤيدة للالتهابات عامل نخر الورم α–وانترليوكين–٦. كذلك انخفضت مستويات الجلوتاثيونالسوبر اكسيددسميوتاز. أدى الإعطاء المتزامن لمستخلص بذور حب الرشاد والكابتوبريل إلى تخفيف الاضطرابات الناجمة عن سمية السيسبلاتين فى إنزيمات الكبد والقلب و كذلك الحالة التأكسيدية والسيتوكين المؤيد للالتهابات.

الاستنتاج: يعد مستخلص بذور حب الرشاد و الكابتوبريل من المواد الوقائية المرشحة بقوة لتخفيف سمية الكبد والقلب المرتبطة بالسيسبلاتين فى الجرزان.