The potential protective effect of alcoholic extracts of some herbs on hepatotoxicity induced by paracetamol in experimental rats

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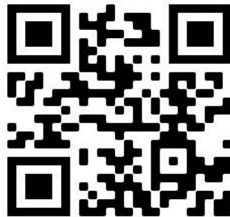

The potential protective effect of alcoholic extracts of some herbs on hepatotoxicity induced by paracetamol in experimental rats.

Abstract

There are many plants which are used as herbs by many people such as *Laurus nobilis* and *Elettaria cardamomum*. The purpose of this study was to find out protective alcoholic Extract's effect of *Laurus nobilis* and *Elettaria cardamomum* on hepatotoxicity induced by paracetamol in experimental rats. 30 healthy adult rats of male albino weighing (150±10 g) were used and divided into 6 equal groups, one of them was kept as a negative control, Group (2): was fed on basal diet as a positive control group, All groups were fed on basal diet + orally doses of herbs as the following: (3 and 4) treated with *Laurus nobilis* extract 100and 200 mg/ Kg b.w. respectively ; (5 and 6) treated with *Elettaria cardamomum* extract 100 and 200 mg/ Kg b.w. respectively Once a day for twenty- eight days on twenty -one day, during the administration of the respective treatments, all animals of groups 2, 3, 4, 5 and 6were administered with paracetamol 400 mg/kg orally for one week. At the end of experiment, biological evaluation was calculated. Liver enzymes, bilirubin, proteins and lipid profile were determined in serum. In liver tissue (GPX, SOD, CAT, MDA and α –TNF) were determined. Livers of rats were histopathologically examined. The results showed that alcoholic extract of *Laurus nobilis* and *cardamomum* improved biological evaluation, liver functions, and antioxidant enzymes compared with positive control groups. It could be concluded that take *Laurus nobilis* and *cardamomum* have markedly protected against the harmful effects of paracetamol on liver.

Key words: *Laurus nobilis, Elettaria cardamomum*, paracetamol, Liver functions and antioxidant enzymes.

INTRODUCTION

As one of the body's most vital organs, liver has vital roles to perform **(Mayuren *et al*., 2010).** To maintain normal physiological function, the liver must be kept in a healthy condition. It is believed that drugs are the primary cause of liver damage, which leads to major medical issues worldwide **(Lakshmi *et al*., 2018).** Paracetamol is recognized as acetaminophen as the greatest usually used painkillers **(Sheen *et al*., 2002).** Paracetamol is known to be relatively non-toxic in a therapeutic dose **(Siemionow *et al*., 2016).** Its toxicity is caused by a lone or frequent high dosage or chronic intake Tittction of the liver and kidneys is regarded as an example many drug therapy troubles **(Cepan *et al*., 2018).** Cytochrome P450 and glucuronidation or sulfations mainly lead to the metabolisation of the swallowed curative dosage of PCM. Fatigued GSH levels are depleted; NAPQI can bind freely to other cellular proteins that are responsible for oxidative stress and necrosis. **(Hamza and Al-Harbi, 2015).** Many diseases can be prevented and improved with the use of herbs and spices. Such as liver disease, which require immediate care and priority treatment modern medicines do not always help to increase renewable activity and prevent fibrosis and cirrhosis development. The search for new drugs including herbal products with a broad range of pharmacological activities and economic affordability has increased in recent years **(Singh *et al*., 2013).**Various researchers have positively evaluated and explored a broad range of pharmacological activities among them *Laurus nobilis* ethanolic extract has antioxidant and wound healing effect **(Vardapetyan *et al*., 2013).** In the treatment of gastrointestines, rheumatism, migraines, and diuretic, antimicroscopic, improving appetite and digestion are also used **(Santos & Rao, 2000).** The volatile laurel oils suppress tuberculosis development and stimulate immunity. Phytoncides are abundant in the leaves of *L. nobilis*, a large number of necessary tannins and trace elements which assistance to control body poisons **(Rukhkyan *et al*., 2013).** *L. nobilis* is help to prevent and treat type II diabetes as lowers blood serum glucose levels. *L. nobilis* lowers total cholesterol (TC) and LDL levels in

body **(Khan *et al*., 2009).** And *cardamomum* is the member of the *Zingiberaceae* family. Its dried fruit is one of the world's most expensive spices. The dehydrated fruit is used as a flavouring agent in whole or in ground form and also for flatulence intake medicines. *Cardamomum* was used in curative herbs for urinary and kidney diseases and in addition to culinary purposes **(Ballabh *et al*., 2008).** *Cardamom* extracts have antimicrobial properties, according to studies. **(Hammad *et al*., 2014 & Winarsi *et al*., 2014)** hepatoprotective activity, anti-hyperlipidemic and antidiabetic effect **(Kandasamy *et al.,* 2010, & Chacko *et al*., 2012).**

Current study is undertaken to examined the protective effects of alcohol extracts of *Laurus nobilis* & *Elettaria cardamomum* on liver toxicity and hematological parameters of rats suffering from hepatotoxicity induced by paracetamol.

Materials and Methods

Materials:

Laurus nobilis and *Elettaria cardamomum* were purchased from the Cairo-based Agricultural Seeds, Herbs, and Medicinal Plants Company. Thirty adult male albino rats (*Sprague Dawley* strain) were procured from the Helwan farm animal colony, Vaccine and Immunity Organization, Ministry of Health, Cairo Governorate, Egypt. El-Gomhoria Company for Trading Drugs, Chemicals, and Medical Appliances, Cairo, Egypt, supplied all essential chemicals. We purchased casein, vitamins, minerals, cellulose, and choline chloride from El-Gomhoria Company in Cairo, Egypt.

Methods:

Chemical analysis of herbs

The polyphenolic compounds of plants extract were fractionated and identified for phenolic compounds by HPLC **(Tarola *et al.,* 2013).**

Preparation of herbs:

Dried herbs were purchased then heated in oven for ten minutes then triturates into a well powder and saved till for preparation alcohol extract.

Preparation of alcohol herbs extract:

Approximately 200 g of ground herbs were steeped for 3 days in 70% ethanol at room temperature (23–25 °C) with intermittent shaking. It went through a muslin cloth and then a Whatman qualitative grade 1 filter paper. The combined filtrates were evaporated on a rotary evaporator at reduced pressure (760 mmHg) after this procedure was done twice **(Chacko *et al*., 2012).**

Experimental animal

Thirty mature white Albino rats of an average body weight 150±10 g of *Sprague Dawley* Strain was used in this study. Rats were fed on basal ration supplying the essential vitamins and trace elements and water supply was given ad-libitum.

Preparation of Experimental diet

Basal diet was prepared from fine ingredient per 100 g as follows: Casein (≥ 80% protein) 14%, Sunflower oil 4 %, salts mixture 4%, vitamins mixture 1%, DL-methionine 0.3%, choline chloride 0.2% which was added at the expense of corn starch up to 100g **(Reeves *et al.,* 1993).**

Experimental design

Rats were divided into six groups 5 animals each as a following:

Group (1): was fed on basal diet as a negative control group (G-).
Group (2): was fed on basal diet as a positive control group (G+).
Groups (3 and 4)**:** were fed on basal diet and treated daily orally with *Laurus nobilis* extract (100 and 200 mg / Kg body weight.
Groups (5 and **6)** were fed on basal diet and treated daily orally with *Elettaria cardamomum* extract (100 and 200 mg / Kg body weight). Once a day for twenty- eight days. On twenty -one day, during the administration of the respective treatments, all animals of groups 2, 3, 4, 5 and 6were administered with paracetamol 400 mg/kg orally for one week according to (**Ravindran *et al.,* 2013).** Body weight and feed intake were checked once a week. At the end of experimental period animals were weighed, fasted overnight, and then sacrificed under very light ether anaesthesia.

Biological evaluation

Body weight gain, feed intake, feed efficiency ratio, and relative organs weight were calculated at the end of the experiment according to **Chapman *et al*., (1959).**

Biochemical analysis of serum:

After sacrifice of rats, blood samplings were collected from hepatic portal vein of each rat in dried clean centrifuge tubes. Serum was carefully separated by centrifugation of blood samples at 3500 round per minute (rpm) for 15 minutes at room temperature, transferred into dry clean ebendorf tubes, then kept frozen at - 20˚C for later determinations.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined according to

Bergmeyer *et al.,* (1986), serum (ALP) was determination according to the colorimetric method of **Roy (1970),** albumin according to **Drupt, (1974)** total protein according to **Sonnenwirth and Jaret, (1980).** Globulin was calculated according to **Busher, (1990)** using the following equation:

Globulin = Total protein – Albumin. Total bilirubin was determined in the serum according to **Doumas *et al*., (1973),** direct and indirect bilirubin were determined in the serum according to **Chary and Sharm (2004)**

Total cholesterol was determined in the serum according to the method described by **Allain *et al*., (1974).** Triglycerides were determined in the serum according to the method described by **Trinder and Ann (1969).** HDL-C was determined in the serum according to the method described by **Lopes- Virella *et al.,* (1977).** Serum LDL-c and VLDL-C were calculated according to **Friedwald *et al.,* (1972).**

Organ sampling:

Livers was removed from rats by careful dissection, washed in saline solution (0.9%), dry using filter paper and independently weighed. A specimen from liver was kept at (-20 °C) for preparation of tissue homogenate for determination of antioxidant parameters. The homogenation was centrifuged at 1000 r.p.m for 10 minutes.

Histopathological examinations

The livers of sacrificed rats were submerged in a 10% formalin solution. After that, the fixed specimens were cut, cleaned, and dehydrated in increasing degrees of alcohol. They were then washed with xylol, fixed in paraffin, sectioned at 4-6 microns thickness, and stained with heamtoxylin and eosin for examination of liver components according to **Carleton (1979).**

Statistical analysis:

Statistical analysis were carried out using one-way analysis of variance (ANOVA) test followed by Duncan test through the program of (SPSS). Results were expressed as mean± SD. The differences among means at $p < 0.05$ were considered significant **(Snedecor and Cochran, 1989)**.

Results

Phenolic compounds of *Laurus nobilis* and *Elettaria cardamomum* by HPLC analysis

Laurus nobilis analyzed for their phenolic Compounds. The obtained results showed in table (1):*Laurus nobilis* recorded higher content of Gallic acid, Catechin, Chlorogenic acid, Naringenin and Ellagic acid while recorded lower content of Syringic acid, Vanillin, Coumaric acid and Pyro catechol.

Elettaria cardamomum analyzed for their phenolic Compounds. The obtained results showed in table (2): *Elettaria cardamomum* recorded higher content of Gallic acid, Chlorogenic acid and Rutin while recorded lower content of Methyl gallate, Vanillin, Cinnamic acid and Naringenin.

Table (1): Phenolic compounds of *Laurus nobilis* (1g/15ml)

	***Laurus nobilis* (1g/15ml)**		
	Area	**Conc. (µg/ml)**	**Conc.(µg/15ml=µg/g)**
Gallic acid	717.20	63.03	945.42
Chlorogenic acid	648.08	48.41	726.22
Catechin	512.49	61.41	921.09
Methyl gallate	1986.88	26.97	404.59
Caffeic acid	204.07	8.72	130.83
Syringic acid	50.28	2.20	33.00
Pyro catechol	49.95	3.54	53.16

Rutin	258.34	35.17	527.48
Ellagic acid	701.10	46.91	703.65
Coumaric acid	180.62	3.07	46.05
Vanillin	134.60	3.03	45.38
Ferulic acid	242.80	8.47	127.10
Naringenin	860.29	47.55	713.28
Taxifolin	278.98	20.28	304.18

Table (2): Phenolic compounds of *Elettaria cardamomum* (1g/15ml)

	***Elettaria cardamomum* (1g/15ml)**		
	Area	**Conc. (µg/ml)**	**Conc.(µg/15ml=µg/g)**
Gallic acid	117.79	10.35	155.27
Chlorogenic acid	62.42	4.66	69.94
Catechin	4.80	0.57	8.62
Methyl gallate	10.85	0.15	2.21
Caffeic acid	24.70	1.06	15.84
Syringic acid	35.01	1.53	22.98
Rutin	22.78	3.10	46.52
Ellagic acid	16.15	1.08	16.21
Coumaric acid	104.24	1.77	26.58
Vanillin	12.03	0.27	4.06
Naringenin	8.70	0.48	7.22
Cinnamic acid	46.96	0.47	7.11

Biological evaluation:

Results of FI, BWG% and (FER) were shown there is significant decrease of these parameters in positive control

compared to normal group. But, there was significant increase in the other treated groups when compared with positive control. Regarding to FI, the best results were found in groups *Laurus nobilis* (100 and 200 mg/kg). The best results for BWG% and FER was recorded for *Laurus nobilis* (200 mg/kg) which recorded non- significant with normal group.

Table (3): Protective effect of *Laurus nobilis* and *Elettaria* on feed intake (FI), body weight gain (BWG %) and feed efficiency ratio (FER) in rats

Parameter / Groups	FI (g/28 day)	BWG (%)	FER
(- ve) Control	507.40 ± 2.23[a]	74.00 ± 3.33[a]	0.145 ± 0.01[a]
(+ve) Control	386.40 ±1.25[e]	40.58 ± 1.39[d]	0.105 ± 0.00[d]
***Laurus nobilis* (100 mg /kg)**	497.40 ± 1.83[b]	62.36 ± 1.56[b]	0.125 ± 0.00[b]
***Laurus nobilis* (200 mg /kg)**	497.20 ± 2.18[b]	71.45 ± 2.72[a]	0.143 ± 0.01[a]
***Elettaria* (100 mg /kg)**	471.20 ± 2.53[d]	53.00 ± 2.23[c]	0.112 ± 0.00[c]
***Elettaria* (200 mg /kg)**	470.80 ± 2.45[d]	55.00 ± 3.80[c]	0.116 ± 0.01[c]

Means in the same column with completely different letters are significantly different at p<0.05.

Relative liver weight:

Positive control group have increase in relative liver weight as compared with negative group. Relative liver weight showed significant decrease in all treated groups as compared to positive control. The best results were found in groups *Laurus nobilis* and *Elettaria* (200 mg/kg) because these treatments showed significant decrease, when compare with other treated groups as shown in (Table 4).

Table (4): Protective effect of *Laurus nobilis* and *Elettaria on* relative liver weight rats (mean ± SD)

Parameter / Groups	Relative Liver weight%
(- ve) Control	2.80 ± 0.01[d]
(+ve) Control	4.20 ± 0.03[a]
***Laurus nobilis* (100 mg /kg)**	3.72 ± 0.02[b]
***Laurus nobilis* (200 mg /kg)**	3.10 ± 0.01[c]
***Elettaria* (100 mg /kg)**	3.75 ± 0.03[b]
***Elettaria* (200 mg /kg)**	3.10 ± 0.01[c]

Means in the same column with completely different letters are significantly different at $p<0.05$.

Liver functions:

Mean values of AST, ALT and ALP in the (+ve) control group showed significant increase as comparison with the (-ve) control group. All treated groups recorded significant decrease in all liver enzymes as compared to control (G+). Best results in ALT and AST were found in rats received *Laurus nobilis* (200 mg/kg) and *Elettaria* (200mg/kg), while *Laurus nobilis* (200 mg /kg) only recorded the best result in ALP.

Table (5): Protective effect of *Laurus nobilis* and *Elettaria* on serum liver enzyme (ALT, AST and ALP) in rats (mean ± SD)

Parameter / Groups	ALT (u/l)	AST (u/l)	ALP (u/l)
(- ve) Control	43.29 ± 1.62[e]	70.33 ± 3.55[d]	137.00 ± 1.89[e]
(+ve) Control	100.31 ±1.37[a]	118.59 ± 1.80[a]	160.46 ± 2.21[a]
***Laurus nobilis* (100 mg /kg)**	60.35 ± 3.04[c]	85.39 ± 1.70[b]	152.16 ± 2.38[bc]
***Laurus nobilis* (200 mg /kg)**	53.41 ± 2.37[d]	77.26 ± 3.71[c]	143.24 ± 2.06[d]

Elettaria (100 mg /kg)	63.49 ± 2.37[b]	86.43 ± 1.65[b]	155.00 ± 3.61[b]
Elettaria (200 mg /kg)	55.50 ± 2.64[d]	74.51 ± 2.75[c]	150.21 ± 3.48[c]

Means in the same column with completely different letters are significantly different at $p<0.05$.

Serum Albumin, Globulin and Total protein

The results revealed that mean value of total protein, albumin and globulin in paracetamol rats group (G+) was significantly decreased as compared with normal group (G-).while All treated groups recorded significant increase as comparison with control (G+). highest level of total protein and globulin recorded by treated group with *Elettaria* (200 mg/kg) ,best result in albumin found in groups *Elettaria* (200 mg/kg) and *Laurus nobilis* (200 mg /kg) as shown in (Table 6)

Table (6): Protective effect of *Laurus nobilis* and *Elettaria* on total protein, albumin and globulin in rats

Parameter / Groups	TP (mg/dl)	Alb (mg/dl)	Glob (mg/dl)
(- ve) Control	7.75 ± 0.01[a]	4.07 ± 0.04[a]	**3.68 ± 0.03[a]**
(+ve) Control	4.86 ± 0.01[f]	2.57 ± 0.02[d]	**2.29 ± 0.04[d]**
***Laurus nobilis* (100 mg /kg)**	5.52 ± 0.04[e]	2.89 ± 0.02[c]	**2.63 ± 0.01[c]**
***Laurus nobilis* (200 mg /kg)**	5.90 ± 0.03[c]	3.20 ± 0.15[b]	**2.70 ± 0.02[c]**
***Elettaria* (100 mg /kg)**	5.74 ± 0.01[d]	2.95 ± 0.01[c]	**2.79 ± 0.01[c]**
***Elettaria* (200 mg /kg)**	6.50 ± 0.22[b]	3.30 ± 0.15[b]	**3.20 ± 0.36[b]**

Means in the same column with completely different letters are significantly different at $p<0.05$.

Total bilirubin, direct bilirubin and indirect bilirubin

The results indicated that mean values of total bilirubin, direct bilirubin and in direct bilirubin in the (+ve) control group were significantly increased as compared with (-ve) control group. All treated groups recorded significant decreased comparison with

(+ve) control group. The best results in total bilirubin and indirect bilirubin found in *Elettaria* (200mg/kg), while groups treated with *Laurus nobilis* (200 mg /kg) and *Elettaria* (100mg/kg) recorded the best result in direct bilirubin.

Table (7): Protective effect of *Laurus nobilis* and *Elettaria* on Total bilirubin, direct bilirubin and indirect bilirubin in rats

Parameter Groups	T.BIL (mg /dl)	D.BIL (mg /dl)	IN.BIL (mg /dl)
(- ve) Control	0.50 ± 0.02[e]	0.13 ± 0.01[d]	**0.37 ± 0.02[d]**
(+ve) Control	1.42 ± 0.02[a]	0.23 ± 0.01[a]	**1.19 ± 0.01[a]**
***Laurus nobilis* (100 mg /kg)**	0.76 ± 0.02[b]	0.17 ± 0.02[b]	**0.59 ± 0.03[b]**
***Laurus nobilis* (200 mg /kg)**	0.61 ± 0.01[c]	0.14 ± 0.01[cd]	**0.47 ± 0.02[c]**
***Elettaria* (100 mg /kg)**	0.63 ± 0.01[c]	0.14 ± 0.02[cd]	**0.49 ± 0.03[c]**
***Elettaria* (200 mg /kg)**	0.55 ± 0.02[d]	0.15 ± 0.02[c]	**0.40 ± 0.03[d]**

Means in the same column with completely different letters are significantly different at p<0.05.

Serum lipid profile*:*

The mean values of cholesterol, triglyceride low-density lipoprotein and very low-density lipoprotein were significantly increased in the (+ve) control rats comparison with the (-ve) control group. All treated groups showed significant decrease (P<0.05) comparing with the (+ve) control rats. The best result was obtained in rats treated with *Elettaria* (200 mg /kg) in Parameter VLDL-c groups Treated with *Elettaria* (200 mg /kg) and *Laurus nobilis* (200 mg /kg) recorded the best result.

The mean values of HDL-c were low in (+ve) control comparison with the (-ve) control rats. All treated groups recorded significant increase (P<0.05) as compared with (+ve) control rats. The best result was obtained in rats treated with *Elettaria* (200 mg /kg).

Table (8): Protective effect of *Laurus nobilis* and *Elettaria* on lipid profile in rats (mean ± SD)

Parameter / Groups	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
(- ve) Control	95.24 ± 1.63[e]	85.00 ± 1.58[e]	51.37 ± 1.57[a]	26.87 ± 2.18[e]	17.00 ± 0.32[d]
(+ve) Control	247.49 ± 1.80[a]	130.00 ± 1.60[a]	37.26 ± 1.55[e]	184.23 ± 2.71[a]	26.00 ± 0.31[a]
Laurus nobilis (100 mg /kg)	143.45 ± 1.55[b]	110.00 ± 1.20[b]	43.49 ± 1.39[c]	77.96 ± 0.85[b]	22.00 ± 0.32[b]
Laurus nobilis (200 mg /kg)	123.00 ± 2.49[c]	102.00 ± 2.00[c]	45.31 ± 1.43[c]	57.29 ± 2.28[c]	20.40 ± 1.58[c]
Elettaria (100 mg /kg)	143.45 ± 1.55[b]	109.00 ± 1.58[b]	41.28 ± 1.49[d]	80.37 ± 3.22[b]	21.80 ± 0.31[b]
Elettaria (200 mg /kg)	100.75 ± 1.66[d]	97.00 ± 1.50[d]	48.37 ± 1.60[b]	32.98 ± 1.73[d]	19.40 ± 1.76[c]

Means in the same column with completely different letters are significantly different at $p<0.05$.

Antioxidant enzymes (GP_X, SOD, CAT, Lipid peroxidation parameter (MDA) and tumor necrosis factor -α (α –TNF) in liver tissue.

Table illustrated activity of liver glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) were significantly decrease in positive control group when comparison with negative control group while increased in all treatment groups when comparison with (+ve) control and best results found in groups treated with *Laurus nobilis* (200 mg /kg) and *Elettaria* (200 mg /kg).

Table (9) also showed that positive control group recorded a significant increase in the mean value of MDA and TNF-α compared with the negative control group while all treatment groups showed significant decrease compared with the (+ve) control rats and the best results found in groups treated with *Laurus nobilis* (200 mg /kg)and *Elettaria* (200 mg /kg).

Table (9): Protective effect of *Laurus nobilis* and *Elettaria* on GP_X, SOD lipids peroxidation MDA, CAT and tumor necrosis factor -α in liver tissue in rats (mean ± SD)

Parameter / Groups	GPx (U/mg)	SOD (U/mg)	MDA (nmol/mg)	CAT (ng/mg)	α -TNF (Pg/mg)
(- ve) Control	200.00 ± 2.00^{a}	205.33 ± 2.51^{a}	2.50 ± 0.100^{d}	15.00 ± 1.00^{a}	**30.0 ± 2.00^{d}**
(+ve) Control	70.00 ± 2.00^{e}	45.00 ± 1.00^{d}	44.00 ± 1.00^{a}	3.06 ± 1.00^{d}	**150.0 ± 2.00^{a}**
***Laurus nobilis* (100 mg /kg)**	174.00 ± 2.00^{d}	170.00 ± 3.00^{c}	10.86 ± 1.00^{b}	6.00± 2.00^{c}	**53.0 ± 3.00^{b}**
***Laurus nobilis* (200 mg /kg)**	190.00 ± 1.00^{b}	190.00 ± 2.00^{b}	6.71 ± 2.00^{c}	10.00 ± 2.00^{b}	**44.0 ± 2.00^{c}**
***Elettaria* (100 mg /kg)**	180.00 ± 2.00^{c}	173.00 ± 3.00^{c}	9.37 ± 1.00^{b}	7.00 ± 1.00^{c}	**50.0 ± 1.00^{b}**
***Elettaria* (200 mg /kg)**	192.00 ± 2.00^{b}	194.0 ± 2.00^{b}	5.00 ± 1.00^{c}	12.00 ± 2.00^{b}	**40.0 ± 4.00^{c}**

Means in the same column with completely different letters are significantly different at $p<0.05$.

Histological Results:

The results obtained from histological liver sections stained with H&EX 400 are illustrated in Fig.1 Liver section show no normal histological structure of hepatic lobules in (- ve) Control group (A). However, liver from paracetamol (+ ve) control group showed congestion of central vein, Kupffer cells activation , vacuolar degeneration of hepatocytes and dilatation with congestion of hepatic sinusoids as well as focal hepatocellular necrosis associated with inflammatory cells infiltration (B),while congestion of central vein and Kupffer cells activation observed in paracetamol + *Laurus nobilis* (100 mg /kg) group (C) when

compared to no histopathological changes except Kupffer cells activation in paracetamol + *Laurus nobilis* (200 mg /kg) group (D). However, exhibited Kupffer cells activation and microvesicular steatosis observed in paracetamol + *Elettaria* (100 mg /kg) group (E). No histopathological changes except Kupffer cells activation observed in *Elettaria* (200 mg /kg) group (F).

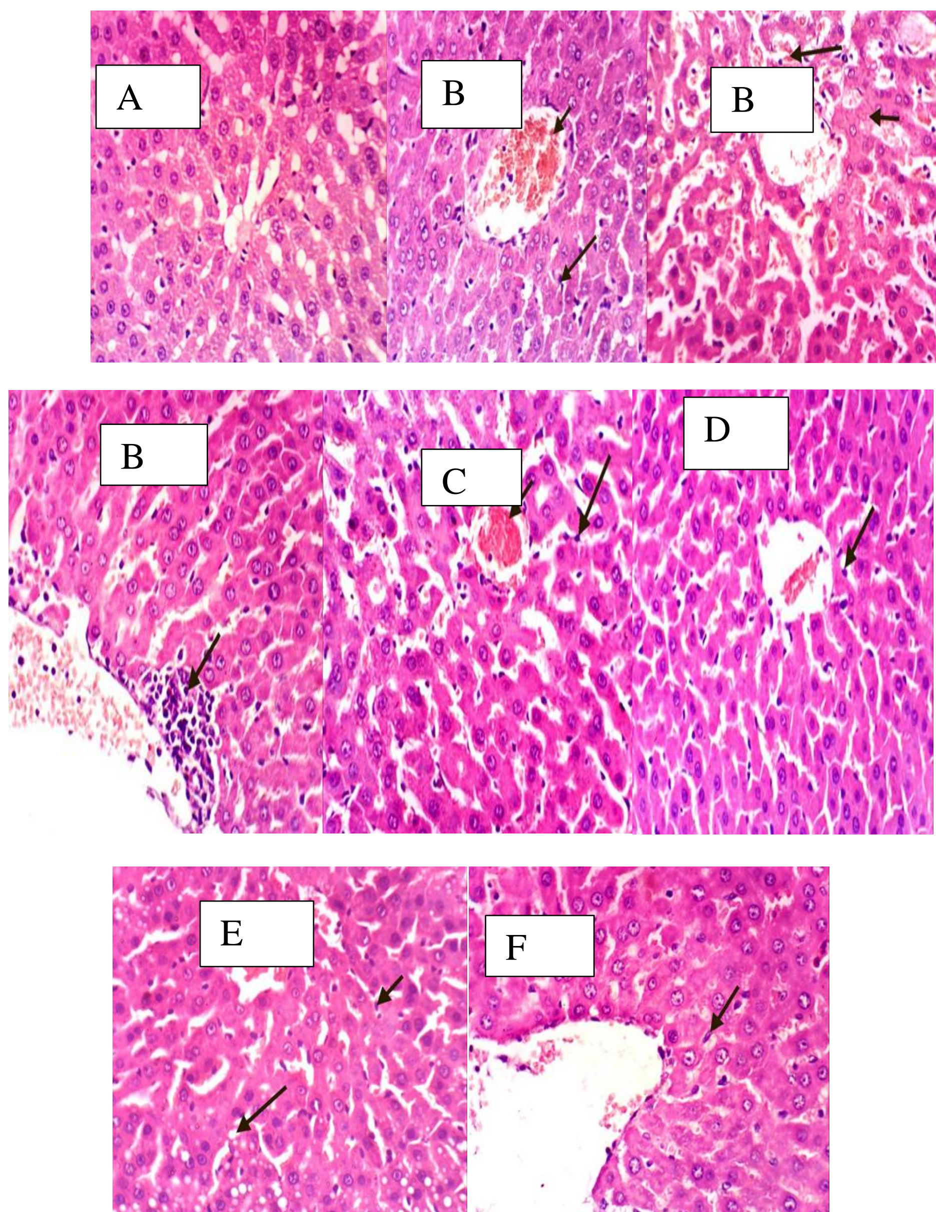

Fig. 1: Microscopic images of hematoxylin and eosin (H & E X 400) stained liver sections showing (A) Normal (-ve) Control group. (B) Paracetamol (+ve) Control group. (C) Paracetamol + *Laurus nobilis* (100 mg /kg) group.

(D) Paracetamol + *Laurus nobilis* (200 mg /kg) group. (E) paracetamol+*Elettaria* (100 mg /kg) group. (F) Paracetamol+*Elettaria* (200 mg /kg) group.

Discussion

Muñiz-Márquez *et al*., (2014) who found that the HPLC analysis showed that presence of *L. nobilis* extract of four phenolic compounds, which responsible for its antioxidant activities: resorcinol, pyrogallol, gallic acid and coumaric acid. Caffeic, vain, and ferulic acids in leaves extracts *L. nobilis* reported by **Muchuweti, *et al*., (2007). Nihal *et al*., (2016)** told about presence of gallic acid, tannic acid, 4, 5-Dicaffeoyl quinic acid and caffeic acid in HPLC extract analyses of cardamomum. Polyphenolic are natural antioxidants, as caffeic acid and gallic acids that decrease oxidation of vital biomolecules **(Beltran-Ramirez *et al*., 2008).**

These findings are in agreement with **Kanchana and Sadiq, (2011)** who concluded that the body weight gain of the group of rats treated with paracetamol is lower than the normal control group. **Dwivedi et al., (2015)** investigated that the bodyweight and feed consumption in the treated group with paracetamol decreased statistically significantly in comparison to normal group. **Adil *et al*., (2016)** told that body weight of acetaminophene rats decreased significantly from normal rats. **Al Chalabi *et al*., (2020)** who noticed that *Laurus nobilis* extract treated group achieved an amelioration in body weight gain comparison with rat suffering from diabetes. **El-Segaeyn *et al*., (2007)** reported that *cardamomum* elements can improve nutrient status and appetite and enhance element metabolism in the *cardamomum* group.

In positive group, hepatic weight is increased and this effect may be caused by hepatic cell inflammatory. In the histopathetic studies of the group treated with paracetamol in the liver tissue, clearly the central vena was dilated with bleeding and the presence of inflammatory cells in hepatic cells, according to the **Dwivedi *et al*., (2015)**. Also, **Kane *et al*., (2016)** investigated the increase in

mean liver weight in all acute acetaminophen-treated groups (as percentage of body weight). In acetaminophene rats, **Adil *et al*., (2016)** who told that relative liver weight was improved comparison with ordinary rats. **Alam *et al*., (2017)** mentioned that a significant increase in relative liver weight of the experimental groups of animals treated with paracetamol compared with normal group.

Those findings are line with **Ahmed *et al*., (2001**) who mentioned that acetaminophen induced hepatotoxicity caused over-production of AST and ALP due to liver parenchymal injuries and increased (ALP) synthesis, which indicated that bile ducts affected ALP in response to cholesterol and increased biliary pressure. In paracetamol administered rats **Ravindran et al., (2013)** found that elevated serum activity of SAT and SAT caused by an increased permeability, damage and/or hepatocytes necrosis. **Sanchez-Valle *et al*., (2012) and Al Chalabi *et al*., (2020)** who mentioned that statistical reduction of the ALT, AST and ALP liver function in diabetic group which gives *Laurus nobilis* alcoholic extract compared to normal control group .The possible mechanism of the results because of the antioxidant compounds in this extract is proof of the diabetes-associated phénomene of fat oxidation and of its effect on necrosis and liver cell damage, thereby regulating the function of the liver. Prevent diabetic liver damage by improving and increasing the activity of antioxidants, leading to a reduction in hepatic lesions markers such as ALT, AST and ALP **(Alam *et al*., 2014). Casamassima *et al*., (2017)** who told decrease of the liver enzymes of ALT and AST was the resulted of dried leaves *Laurus nobilis* meals. **Girish *et al*., (2009)** who told that the *cardamomum* activity of the ALT, AST, and ALP enzymes has decreased significantly. This may be because the extracts protect hepatic cells and preserve their functional integrity. **Darwish and Abd El Azime, (2013)** found that AST, ALT, and ALP levels were reduced, indicating hepatoprotective effects by treatment with extract of *Elettaria cardamomum* seeds.

This finding are emphasized by **Elkomy *et al*., (2016)** told that administration of paracetamol by oral caused significantly lower levels of albumin when comparison with the normal rats. **Mohammed *et al*., (2021)** mentioned that albumin and total protein in *L. nobilis* extract group are insignificantly increased comparison to diabetic group of rat. **Aboubakr and Abdelazem, (2016)** who revealed that aqueous extract of *cardamomum* increased the lowered serum level of albumin in hepatotoxicity rats induced by gentamicin.

The results are supported by **Hegde and Joshi, (2010)** who indicated that the administration of acetaminophen caused hepatic abnormalities by significant increases in total bilirubin and direct bilirubin level hyperbilirubinemia caused by biliary tract obstruction and heme destruction. **Ravindran *et al*., (2013)** observed a substantial increase in serum bilirubin levels compared to all other treated groups with paracetamol intoxicated rats. Higher bilirubin levels are an indication of biliary obstruction and hemolysis a consequence of a reduced hepatocyte blood supply. **Parekh and Klag , (2001**) who told that *L. nobilis* methanol extract treatment significantly reduces increased serum liver enzymes and bilirubin levels to almost normal levels, which could be the result of membrane of plasma stabilization and preserving of functional state of liver of paracetamol toxicity. **Mahmood *et al*., (2014)** who reported that cardamomum extract has significantly decreased total bilirubin in serum towards normal which indicate that cardamomum has anti-hepatotoxic effect.

Results supported by **Rajkapoor *et al*., (2008)** & **Elkomy *et al*., (2016)** mentioned that comparison with normal control groups the oral administration of paracetamol has led to a considerable decrease in HDL-c. HDL-Cholesterol attributed to the overproduced of H2O2generated during microsomal metabolism of paracetamol generated during the cytochrome P450. **Honmore *et al*., (2015)** who cleared that administration of acetaminophen increases the total serum cholesterol, LDL and triglyceride and decreases the HDL level significantly. Because the lipoprotein and cholesterol metabolism have been impaired by

acetaminophen. **Casamassima *et al*., (2017)** mentioned that significant decrease in the lipid profile of the blood and increased HDL were the result of dried *L. nobilis* on meal. **Al Chalabi *et al*., (2020)** who indicated that decreased cholesterol concentration, TG, LDL and VLDL in diabetic groups treated with alcoholic extract of *Laurus nobilis* this is may be due to flavonoids found in *Laurus nobilis* which participated in lipid profile management, or could relate to the role of laurel leaves in decreasing the concentration of cholesterol. **Chbili *et al*., (2020)** recommended *L. nobilis* tea in healthy volunteer groups to improve blood lipid profile (increased HDL level and reduced triglycerid and LDL levels) and have possible positive effects on reducing risk for coronary heart disease (**Musa *et al*., 2011** and **Titilayo *et al*., 2018**). **Shobana and Naidu, (2000)** and **Sadeek and Abd el-Razek, (2010**) indicated that cardamomum decreased in cholesterol and triglyceride concentrations has reflected its protective hepatocellular effects because cardamomum has phenolic compounds and essential oil which reduce the hyperlipidemia. **Darwish and Abd El Azime, (2013)** found that serum triglyceride and cholesterol levels in the diet of rats receiving cardamomum are attributed to inhibition of hepatic – HMG CoA reductase activity. In addition to its effectiveness in reducting LDL-c susceptibility to oxidation. **Aboubakr and Abdelazem, (2016)** who revealed that significant improvement in HDL-c, serum levels in cardamomum aqueous extract in hepatotoxicity rats induced by gentamicin

Ravindran *et al*., (2013) who observed that rats treated with paracetamol significant reduction in SOD activity in tissues and erythrocytes this decline could be due to inefficient ROS scavenging which could be involved in the in activation of oxidative enzymes. **Sakran *et al*., (2014)** told that liver and total plasma antioxidant GPx, CAT and SOD in the Paracetamol group decreased significantly from their normal control group and the concentration of MDA increased markedly comparison with the standard control group. **Honmore *et al*.,(2015)** studied that acetaminophen administered significantly decreased SOD and increased MDA in hepatic tissue due to toxicity induced by the

acetaminophene, increased peroxidation of free radicals and/or decreased antioxidant protection system activity. **Rathee *et al*., (2018**) have shown that a significant increase is observed in paracetamol group comparing with standard control group in oxidative stress malondialdehyde and inflammatory mediators. Also, **Mallikarjuna *et al*., (2008**) told that reduction in catalase activity during the ingestion of paracetamol which caused by inefficient scavenging of H_2O_2. **Ravindran *et al*., (2013)** who investigated that a significant modulation of antioxidant modulation by co-administration of methanolic extract of *Laurus nobilis* in erythrocytes, plasma, and tissue with paracetamol to suggest an enhanced effect of *Laurus nobilis* on cellular antioxidant defence Elevation of antioxidant status presumably provides a protection against the peroxidation of lipids by quenching and detoxifying free radicals that almost normalize them. **Yadav and Bhatnagar, (2007)** reported *cardamomum* inhibits lipid peroxidation because it's strong reducing power and superoxide radical scavenging activity. *Cardamomum* has a significantly lower level of MDA in irradiated animals and increases the activity of antioxidant enzymes SOD & CAT. **Nihal *et al*., (2016)** reported that *cardamomum* treatment decreased liver damage and also significantly inhibited the formation of hepatic MDA as well as increased antioxidant enzyme activities in the liver such as SOD , GPx and catalase CAT in the hepatic of diethylnitrosamine treated rats due to antioxidant effect of cardamomum and has inhibit of inflammatory markers.

Conclusion

Paracetamol has toxic side effects on experimental animals proved by biochemical and histological results. The results concluded that using high doses of alcoholic extracts of *Laurus nobilis* and *Elettaria cardamomum* improved liver function and hematological parameters so we recommended people to use *Laurus nobilis* and *Elettaria cardamomum* as spices or tea to benefit from their health benefits.

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التأثير الوقائي المحتمل للمستخلصات الكحوليه لبعض الأعشاب على التسمم الكبدي المحدث بالباراسيتامول في فئران التجارب.

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المستخلص العربي

يوجد العديد من النباتات التي يستخدمها الكثيرون من الناس كتوابل مثل اللورا و الحبهان (الهيل) ، أجريت الدراسة الحالية لمعرفة التأثير الوقائي للمستخلصات الكحوليه لكلا من ورق اللورا والحبهان بتركيزين مختلفين (100و 200 مجم / كجم من وزن الجسم) على السمية الكبدية التي يسببها الباراسيتامول (400 مجم / كجم من وزن الجسم) في فئران التجارب. تم استخدام 30 فأر تتراوح أوزانهم بين (150 ± 10 جم). وتم تقسيم الفئران إلى 6 مجموعات متساوية تركت أحد المجموعات كمجموعة ضابطه سالبه ، المجموعة (2) تم تغذيتها علي الغذاء القياسي كمجموعة ضابطه موجبة ، جميع المجموعات الأخري تم تغذيتها علي الغذاء القياسي بالإضافه إلي جرعات من الأعشاب عن طريق الفم كالاتي : المجموعه (3 و 4) تم إعطائهم ورق اللورا بتركيزين (100و 200 مجم / كجم من وزن الجسم) ، و المجموعه (5 و 6) تم إعطائهم الحبهان بتركيزين (100و 200 مجم / كجم من وزن الجسم) وذلك يوميا لمدة 28 يومًا ، وفي اليوم الحادي والعشرين بالإضافة لمستخلصات الأعشاب تم إعطاءالمجموعات (2 ، 3 ، 4، 5 ، 6)الباراسيتامول بتركيز (400 مجم / كجم من وزن الجسم) عن طريق الفم لمدة أسبوع. في نهاية فترة التجربة تم حساب التقييم البيولوجي. كما تم تقدير مستوي إنزيمات الكبد والبيليروبين والبروتينات ودهون الدم في السيرم ومضادات الأكسدة وعامل النخر في أنسجة الكبد. أظهرت النتائج أن المستخلص الكحولي لورق اللورا و الحبهان أدي إلي حدوث تحسن في التقييم البيولوجي ومستوي إنزيمات الكبد ومضادات الأكسدة مقارنة بالمجموعة الضابطة الموجبة. يمكن أن نستنتج أن تناول مستخلصات أوراق اللورا والحبهان يحميان الكبد بصوره ملحوظه من الآثار الضارة للباراسيتامول.

الكلمات المفتاحية: اللورا، الحبهان، الباراسيتامول، وظائف الكبد، الإنزيمات المضاده للأكسدة