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HEPATOPROTECTIVE AND ANTIOXIDANT EFFECTS OF FICUS CARICA AGAINST HEPATOTOXICITY INDUCED BY CCL_4 IN RATS

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ABSTRACT In the view of presumably hepatoprotective potential, effects of water and ether extract of fruits of *Ficus carica L.* (Moraceae) on some serum biochemical parameters, some antioxidant enzymes and liver histopathological picture on CCl_4 induced hepatotoxicity in male albino rats were scrutinized. The results had shown significant reduction in enzymatic values of AST, ALT, ALP, GGT, total bilirubin and lipid peroxidation level (LPO) in liver homogenate in both water extracts of *Ficus carica* (WEF) and ether extracts of *Ficus carica* (EEF) treated groups when compared to the CCl_4 administered group. Moreover, total protein, albumin and globulin levels were significantly increased plus antioxidant scavenging capacity was restored through a significant elevation in reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) activities in liver tissue homogenates in comparison to CCl_4 administered rats. It was clear from the documented results that *Ficus carica* boasts a hepatoprecautionary role against experimentally induced liver cirrhosis by CCl_4.

KEYWORDS : *Ficus carica*, hepatoprotective, antioxidant activity, histopathological picture, Ccl4

Introduction:

The last decade had shown that herbal drugs have the importance and popularity as they considered to be safe, effective and their performance are unquestionable. Plant outcome uses are numerous, hepatoprotective effect is one of the most important, will documented benefit in phytomedicine. Needless to say, there is a constantly increasing require for secure hepatoprotective agents ***(Roy et al., 2012).***

A long history of use of medicaments supposed to be natural in the treatment of liver disorders has been established all over the world, the medicinal plants and their subsidiary products are still used for this reason. Scientific analysis of plants has often shown that the active principles belonging to the plants play a magnificent role in the curative triumph. A variety of restorative plants have been evaluated and found to encompass active principles with therapeutic properties against many diseases. Phenols, essential oils, carotinoids, coumarins, monoterpenes, flavonoids, glycosides, xanthines, among others, are chemical constituents that were found in liver protective plants. For that reason, hepatoprotective drugs formulated from plant origin have given the permission to be introduced in the global market ***(Kumar 2012).*** Insufficient man-made drugs are used in the treatment of liver malfunctions, besides, they can have consequential side effects, for that reason, many people in the world counting those in developed countries reverse their directions to complimentary and replacement medicine ***(Mitra et al., 2000).***

The common fig (*Ficus carica*) is a sundry scattered small deciduous sapling in the mulberry phylum. As one of the first plants grown by human, this plant raised in a wide range of habitats, mainly in the Middle East and Western Asia countries and has been an important food pedigree for long time ago. Whilst the fig is widely known for its wholesome fruit, it had been also used medicinally for centuries before its pharmacological values were well-legitimated via a scientific appraisal. A plenty of experimentations have now outlined the pharmacological activities of fig. By way of illustration, the leaves evince antibacterial, antiviral, hepatoprotective, hypotriglyceridaemic, and cholinesterase inhibitory assets *in vitro* and *in vivo* ***(Perez et al., (1999), Gond and Khadabadi (2008), and Orhan et al., (2011)).*** Special more, fig leaves have anti-inflammatory and antioxidative activities and are potent against various inflammatory disorders such as hemorrhoids and insect stings and bites. The physiological activities of the latex are also very adaptable and have been used in long-established medicine to treat gout, ulcers, and skin diseases such as warts and viruses ***(Bahlooli et al., (2007), Aref et al., (2010), and Lazreg et al., 2011)).*** The volatile composites and the organic acids of fig have antioxidative and acetyl cholinesterase inhibitory effects ***(Oliveira et al., 2010),*** taking into consideration the fact that its proteolytic smattering, ficin, displays antifungal and anthelmintic activities ***(Richter et al., 2002).*** On the top of that, one of the components having a biological effect, 6-Oacyl- β-D-glucosyl-β-sitosterol, has been separated from the latex and hinders proliferation of human cancer cells ***(Rubnov et al., 2001).***

In conventional medicine, the roots of *Ficus carica* are used in treatment of leucoderma and ringworms and its sweet fruits, have antipyretic, purgative, aphrodisiac attributes and have shown to be useful in inflammations and paralysis. *Ficus carica* is declared to be useful in liver and spleen disorders, to heal piles and in the treatment of defective metabolism of uric acid (Patil HYPERLINK "http://ascidatabase.com/author.php?author=Vikas%20V.&last=Patil"and HYPERLINK "http://ascidatabase.com/author.php?author=Vikas%20V.&last=Patil" Vijay 2011).

This work aimed at assessing the hepatoprotective effect of water and ether extracts of *Ficus carica* fruits against hepatotoxicity induced by CCl_4 in male albino rats based on evaluating some serum biochemical parameters, with special remark about their ameliorative effect on oxidative tension caused by CCl_4 and histopathological changes on the liver tissues.

Materials and Methods:

Plant material : *Ficus Carica* fruits were harvested from a garden at the EL Garaisha village in south of Abu Hammad city Sharkia, Egypt.

Standard : Silymarin powder capsules 140 mg was obtained from MADAUS GmbH, Germany.

Experimental animals:

Twenty five adult male albino rats of 150-180 gm average body weight for each were obtained from farm of Faculty of Veterinary Medicine, Zagazig University. All animals were retained under observation and acclimatization period of 14 days in the laboratory environment before starting the experimental time and kept in metal cages in good hygienic conditions. Rats received care in compliance with the guidelines of the National Institute of Health (NIH).

Preparation of *Ficus carica* fruits extracts:

Water extract of *Ficus carica* fruits (WEF) according to ***Jowari et al., (2011):*** One kilogram of *Ficus carica* fruits (fig) was washed cut into small pieces, dried in oven at 40 °C. then grinding by applying a mixer, after that, mixed with two liters of water for 48 h. with periodical shaking. After 48 h. extract was filtered and put in rotator evaporator (Buchi 124 rpm) at 60 °C, 100 mbar pressure and 100 rpm. The extract was lyophilized after releasing from evaporator and the lyophilized sample (yield was 100 gm) kept in vessel in refrigerator at 4 °C.

Ether extract of *Ficus carica* fruits (EEF) according to ***Palaniyppan et al., (2013):*** One kilogram of *Ficus carica* fruits (fig) waswashed then cut into small pieces, dried in oven at 40 °C. then grinding by using a mixer, after that, mixed with two liters of 100% ethyl alcohol for 48 hours with periodical shacking. After 48 hours, the extract was filtered applying gauze and funnel. Evaporation of ethyl alcohol by rotator evaporator (Buchi 124rpm) at 60° C, 100 mbar pressure and 100rpm. The extract was then lyophilized after releasing from evaporator. The lyophilized semisolid mass sample (yield was 100gm) was collected and stored in air tight vessel and kept in refrigerator at 4° C.

The experimental design: Twenty five adult male albino rats were divided into five groups of five rats each.

Control group: Olive oil (1.5mg/kg) was injected intraperitoneally (I.P.) 3 times a week for 9 weeks.

CCl_4 group: 1.5mg/kg Carbone tetrachloride was diluted in olive oil (1:7) and injected I.P. 3 times a week for 9 weeks.

CCl_4+Silymarin group: Silymarin (25mg/kg) diluted in distilled water and was given orally+1.5mg CCl_4 in olive oil 3 times a week for 9 weeks.

CCl_4+WEF: *Ficus carica* water extract (400mg/kg) diluted in 2ml distilled water and was given orally+1.5mg CCl_4 in olive oil 3 times a week for 9 weeks.

CCl_4+EEF: *Ficus carica* ether extract (400mg/kg) diluted in 2ml distilled water and was given orally+1.5mg CCl_4 in olive oil 3 times a week for 9 weeks.

The dose of control and carbon tetrachloride calculated according to ***Khan and Alzohairy (2011).*** The dose of *Ficus carica* was calculated according to ***Adeneye et al., (2009)*** and the dose of silymarin according to ***Khodeary et al., (2009).***

At the end of the experiment, the overnight fasted rats were sacrificed and the following samples were collected:

1) Blood was collected and enabled to clot and serum was separated by centrifugation at 3000rpm/15minutes for determination of serum biochemical guidelines.
2) Liver samples were kept frozen at -70ºC for assessment of tissue free radical scavenging activities; other liver samples were fixed in 10% formalin for histopathological examinations.

Serum Biochemical Parameters:

Serum aspartate aminotransferase (AST), and alanine aminotransfe rase (ALT) values were quantified colorimetrically according to ***Tietz)1967).*** Alkaline phosphatase (ALP) was measured colorimetrically as stated by ***Belfield and Glodberg (1971).*** Gamma glutamyl transferase activity (GGT) principally evaluated as stated by ***Kaplan and Pesce (1992).*** Serum total proteins were determined according to ***Henry (1964),*** while serum albumin was determined as claimed by ***Doums and Biggs (1976).*** Serum globulin was calculated as the difference between total proteins and albumin. Serum total and direct bilirubin were estimated according to ***Walters and Gerarde (1970).*** Serum indirect bilirubin was calculated as the difference between total and direct bilirubin

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Antioxidant Status and Oxidative Stress Assay:

The -70ºC stored liver samples were used for assessment of reduced glutathione (GSH) level that was assessed spectrophotometrically as stated by ***Sedlak and Lindsay (1968),*** catalase (CAT) enzyme activities ***(Aebi 1974),*** superoxide dismutase (SOD) levels ***(McCord and Fridovich 1969)*** and lipid peroxidation (LPO) contents after a method described by ***Nielsen et al., (1997).***

Histopathological examination of liver:

Samples from the liver of all groups were collected and fixed in 10% neutral formalin for 24 h. before routine processing in paraffin wax. Samples were cut into sections of about 5 microns thickness according to ***(Culling 1974).*** Samples stained using Hematoxylin & Eosin (H&E) and examined microscopically as stated by ***(Bancroft and Stevens 1996).***

Data analysis:

Data were scanned using computers SPSS programs version 21 (2011), the biochemical estimation results reported as Mean ± S.E.M (Standard error of mean). The statistical method was one way anova test, LSD test (least significant difference). Significance probability levels of less than 0.05 were considered significant

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Results

The obtained results reviewed a significant increase (P≤0.05) in serum AST, ALT, ALP and GGT activities (Table 1), in CCL_4 treated group compared to control one. While there was a significant reduction in the aforementioned values in CCL_4+silymarine treated group compared to the CCL_4 administered group. These values were significantly reduced in water and ether extracts of *Ficus carica* viewing the fact of high values of CCL_4 administered group.

Table (1): Effect of *Ficus carica* water and ether extracts on serum AST, ALT, ALP and GGT in rats treated with carbon tetrachloride in male albino rats using silymarin as standard (M±SE) (n=5)

Parameters Group	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
CONTROL	185.2±1.66^{d}	43.8±1.20^{c}	186.4±5.02^{c}	4.56±0.39^{b}
CCL4	299.2±6.65^{a}	84.2±1.36^{a}	456.2±9.76^{a}	12.60±0.75^{a}
SILYMARIN	217.6±1.12^{c}	54.6±0.75^{b}	217.6±4.12^{b}	4.18±0.21^{b}
WEF	243.6±5.30^{b}	52.8±0.92^{b}	172.4±2.18^{c}	4.96±0.18^{b}
EEF	227.4±1.83^{b}	48.2±1.16^{b}	195.6±1.47^{c}	4.10±0.21^{b}

Our data exhibited a significant reduction (P≤0.05) in serum total proteins, albumin and globulin values in CCL_4 treated group compared to control one (Table 2). Treatment with silymarin signified an increase in these values in comparison to CCL_4 administered group. Water and ether extracts of fig. showed similar results as those obtained in control group as well as silymarin treated group.

Table (2): Effect of *Ficus carica* water and ether extracts on serum total protein, albumin, globulin and A/G ratio in rats treated with carbon tetrachloride in male albino rats using silymarin as standard (M±SE) (n=5)

Parameter Group	T. Proteins (gm/dl)	Albumin (gm/dl)	Globulin (gm/dl)	A/G ratio
CONTROL	6.66±0.07^{a}	3.9±0.05^{a}	2.76±0.08^{b}	1.42±0.05^{a}
CCL_4	5.5±0.15^{b}	2.88±0.06^{c}	2.62±0.20^{c}	1.13±0.10^{b}
Silymarin+ CCL_4	6.66±0.11^{a}	3.78±0.04^{ab}	2.88±0.12^{ab}	1.32±0.06^{ab}
WEF+ CCL_4	6.54±0.10^{a}	3.52±0.04^{ab}	3.02±0.12^{ab}	1.17±0.05^{b}
EEF+ CCL_4	6.58±0.04^{a}	3.48±0.04^{b}	3.10±0.07^{a}	1.13±0.04^{b}

Compared to control animals, CCL_4 administered rat's revealed significant elevation (P≤0.05) in serum total bilirubin, direct and indirect bilirubin levels. These values tend to decrease in all tested groups and showed non significant changes compared to control group, the water extract was superior to silymarin treated rats (Table 3).

Table (3): Effect of *Ficus carica* water and ether extracts on serum bilirubin (total, direct and indirect) in rats treated with carbon tetrachloride in male albino rats using silymarin as standard.(M±SE) (n=5)

Parameters Group	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	Indirect Bilirubin (mg/dl)
CONTROL	0.33±0.03^{c}	0.12±0.01^{c}	0.21±0.02^{c}
CCL4	0.81±0.02^{a}	0.26±0.01^{a}	0.55±0.02^{a}
Silymarin+ CCL_4	0.47±0.03^{b}	0.16±0.01^{b}	0.31±0.03^{b}
WEF+ CCL_4	0.36±0.02^{c}	0.11±0.01^{c}	0.25±0.03^{bc}
EEF+ CCL_4	0.39±0.04^{bc}	0.15±0.00^{b}	0.24±0.04^{bc}

Antioxidant Status and Oxidative Stress Assay:

Results of biochemical tests of GSH, CAT, SOD and LPO are shown in Table (4). In CCL_4 administered group, there was a marked depletion ($P \leq 0.05$) in antioxidant enzymes GSH, CAT and SOD along with increase in lipid peroxidation as compared to control rats. Silymarin plus CCL_4 treated group decreased LPO levels and significantly restored antioxidant capacity. Ether extract of *Ficus carica* showed similar results as silymarin group while the values of water extract treated rats showed less antioxidant scavenging activities.

Table (4): *Effect* of *Ficus carica* water and ether extracts on liver GSH, CAT, SOD and LPO in rats treated with carbon tetrachloride in male albino rats using silymarin as standard (M±SE) (n=5)

Parameter Group	GSH (µmol /gm tissue)	CAT (Unit/gm tissue)	SOD (µmol /gm tissue)	LPO (µmol MDA/gm tissue)
CONTROL	14.96±1.28^{a}	8.02±0.63^{a}	0.83±0.092^{a}	5.8±0.70^{d}
CCL_4	9.46±0.66^{d}	5.80±0.12^{c}	0.41±0.05^{c}	30.4±3.10^{a}
Silymarin+ CCL_4	13.36±1.34^{b}	7.77±0.35^{a}	0.85±0.12^{a}	13.8±1.97^{c}
WEF+ CCL_4	11.86±1.18^{c}	6.49±0.32^{b}	0.62±0.11^{b}	23.7±2.07^{b}
EEF+ CCL_4	13.12±1.75^{b}	7.46±0.27^{a}	0.79±0.085^{ab}	15.4±2.93^{c}

Histopathological Examination:

Administration of CCl_4 (1.5 ml/kg b.wt. i/p) 3 times a week for 9 weeks showed a marked hepatic damage which was observed from a marked dilated central vein filled with red blood cells and surrounded by cords and rows of hepatocytes (Fig.1A), massive areas of fatty changes of the liver cell with increased vacuolated cytoplasm and aggregation of inflammatory cells (Fig.1B). Administration of silymarin with CCl4 showing nearly normal central vein surrounded by a normal hepatocytes and scattered aggregates of inflammatory cells (Fig.1C). local edema, few fibroblasts with newly formed blood vessels were seen in some portal areas and interlodular spaces with cords and rows of normal hepatocytes (Fig.1D). Treatment with of water extract of *Ficus carica* (400mg/kg) diluted in 2ml distilled water orally administered +1.5mg CCl_4 in olive oil 3 times a week for 9 weeks showed moderate congestion of the central vein surrounded by cords and rows of normal hepatocytes (Fig.2A). There was a mild congestion of the central vein and mild fatty changes of the hepatocytes (Fig.2B). Liver sections of rats treated with ether extract of *Ficus carica* (400mg/kg) diluted in 2ml distilled water orally administered +1.5mg CCl_4 in olive oil 3 times a week for 9 weeks showing mild congestion of the central vein (Fig.2C). There was a mild congestion of the central vein with the disappearance of fatty changes from the liver cells.

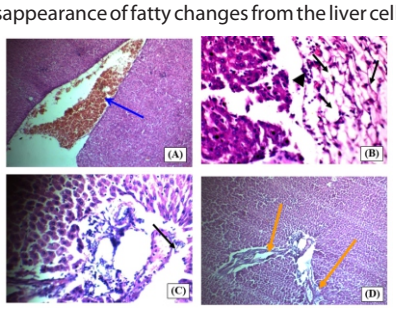

Fig. (1): A) Liver section of rats treated with CCl4. Photomicrograph of hepatic tissue showing markedly dilated central vein filled with red blood cells and surrounded by cords and rows of hepatocytes. (H&E X 200). **B**) Liver section of rats treated with CCl4. Photomicrograph of liver tissue showing massive area of fatty changes of the liver cell with vacuolated cytoplasm and aggregation of inflammatory cells. (H&E X 400). **C**) Liver section of rats treated with silymarin. Photomicrograph of liver tissue showing a nearly normal central vein surrounded by normal hepatocytes and scattered aggregates of inflammatory cells. (H&E X 400). **D**) Liver section of rats treated with silymarin. Photomi¬crograph of hepatic tissue showing nearly normal central vein surrounded by cords and rows of normal hepatocytes. (H&E X 200)

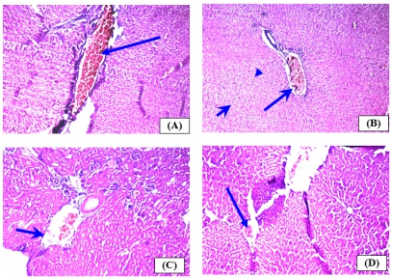

Fig. (2): A) Liver section of rats treated with water extract of fig. Photomicrograph of hepatic tissue showing moderate congestion of the central vein surrounded by cords and rows of normal hepatocytes. (H&E X 200) . **B**) Liver section of rats treated with water extract of fig. Photomicrograph of hepatic tissue showing mild congestion of the central vein and mild fatty changes of the hepatocytes. (H&E X 200). **C**) Liver section of rats treated with ether extract of fig. Photomicrograph of hepatic tissue showing mild congestion of the central vein. (H&E X 200). **D**) Liver section of rats treated with ether extract fig. Photomicrograph of hepatic tissue showing mild congestion of the central vein with disappearance of fatty changes from the liver cells. (H&E X 200)

Discussion

Being the first utmost organ to be revealed to ingested poisons due to its portal blood supply, liver with laying out defensive abilities to the other parts of the body is facing an increased feasibility of hepatic injury ***(Moslen et al., 1996).***

One of the most familiar causes of drug-generation failures and the drugs withdrawn from the market is its capability to cause disadvantageous effects to the liver. These adverse effects can vary gigantically in severity, leading to many possible drug-influence liver injuries ***(Hewitt et al., 2013).*** As a result, it is not surprising that many personals in the world, including those in developed countries decisively turning complimentary and alternative medicine.

The present study aimed at evaluating the hepatoprotective effect of *Ficus carica*, water and ether extracts, against carbon tetrachloride induced hepatotoxicity using silymarin as a standard hepatoprotective drug.

The carbon tetrachloride (CCl_4) is a discriminating hepatotoxic chemical agent induced hepatic cell damage. CCL_4 toxicity is ascribable to reactive free radical (Ccl_3), which is generated by its reductive metabolism by hepatic cytochrome P_{450}s. These reactive free radicals commence cell damage via attaching to cell membrane lipids and lipid peroxidation ***(Kanter et al., 2003).***

Hepatic cells get involved in an array of metabolic activities and contain enzymes which have been used as markers for any hepatic distress such as AST, ALT, ALP and GGT, which considered as an important enzymes to be kept under surveillance for assessing liver malfunctions ***(Hukkeri et al., 2002).***

In the present study, administration of CCl_4 (1.5 ml/kg b.wt. I.P.) 3

times a week for 9 weeks originated a significant hepatic damage which was noticed from the substantial increase in the activities of serum AST, ALT, ALP and GGT. This is a marker of cellular leakage and loss of functional integrity of cell membranes of hepatic cells. This study supported by ***Althnaian et al., (2013)*** who found that i/p injection of CCl_4 markedly affected the liver specific enzymes. They observed a significant increase in serum AST, ALT and ALP activities of CCl_4 treated rats.

Our results revealed that water and ether fig extracts (400 mg/kg b.wt. orally) with CCl_4 (1.5 ml/kg b.wt. I.P.) 3 times a week for 9 weeks generated a hepatoprotective effect against CCl_4 induced hepatic damage. This was observed through assessing liver enzymes activities which showed a remarkable decline in activities of serum AST, ALT, ALP and GGT.

Administration of *Ficus carica* plant extracts showed a significant decrease in the activities of liver enzymes, which could be explained as a consequence of the stabilization of the hepatocyte membrane as well as the hepatic tissue damage repair. This supposition is supported by the view that serum levels of AST, ALT, ALP and GGT return to normal with the curing of hepatic parenchyma and regeneration of hepatocytes.

These results supported by those of ***Krishna et al., (2007),*** the methanol extract of the of *Ficus carica* treated rats suffering a liver damage induced by carbon tetrachloride showed a reduction in serum levels of AST and ALT.

The present data were in agreement with those of ***Adeneye et al., (2009)***, the liver damage was chemically induced by CCl_4 at a single i.p. dose of 1.5 ml/kg of CCl_4. Induction of hepatotoxicity with CCl_4 was characterized by a significant rise in the serum levels of ALT and AST compared to these values in control animals. Groups pretreatment with 100, 200, and 400 mg/kg/day orally of aqueous extract of fig showed a decline in the serum levels of these marker enzymes.

In the same area of interest, a study was performed by ***Aghel et al., (2011),*** a groups of mice received different doses of ethanol extract of *Ficus carica,* (200, 400 and 800 mg/kg), prior to administration of CCl_4. Liver markers such as ALT and AST were increased significantly in CCl_4 treated mice. In groups pretreated with the plant extract and intoxicated with CCl_4, a decreased activity of these two enzymes were observed**.**

The liver synthesizes operational proteins that would be functional within the hepatocytes as well as the ones to be circulated to other parts of the body. Among these export proteins, serum albumin, is the most important protein to be synthesized. Circulated proteins are created on polyribosomes bound to rough endoplasmic reticulum of hepatocytes, with a reversed relationship, proteins destined for intracellular use are synthesized on a free instead of bound polyribosomes ***(Podolosky and Isselbacher 1991).*** Albumin considered as the most abundant protein in animal serum, transporting hormones, fatty acids and other compounds, buffers pH among other functions and hypoalbuminemia in hepatocellular disorders, appearing as an inflammatory response of liver.

In this work, administration of CCl_4 1.5 ml/kg b.wt. I.P. 3 times a week for 9 weeks evoked a significant hepatic damage which was distinguished from the decrease in the activities of serum albumin, total proteins, globulin and A/G ratio. This decrease is attributable to disassociation of polyribosomes from endoplasmic reticulum after CCl_4 administration ***(Clawson 1989).*** Our results were assisted by those of ***Rajesh and Latha (2004)*** and ***Shih et al., (2005),*** the authors found that liver damage produced after chronic CCl_4 administration resulted in significant reduction in serum total proteins and albumin levels. Moreover, ***Abdel Aziz et al., (2014)*** found a significant reduction in serum albumin, total proteins and globulin levels following CCl_4 administration.

The treatment with water and ether extract of fig (400 mg/kg b.wt.) 3 times a week for 9 weeks showed a significant elevation in the levels of serum albumin, total proteins and globulin when compared with CCl_4 administered group.

The present data were substantiated by those of ***Adeneye et al., (2009),*** the authors found that CCl_4 hepatic cirrhosis induction was associated with significant decrease in the serum levels of albumin and total proteins. The decrease could have evolved from the ruinous effect of the toxicant on the hepatic syntheses of these proteins. Pretreatment with aqueous extract of fig protected the liver from the damaging effect of the toxicant by improving the circulating levels of albumin and total proteins. The extract could fortify the protein synthetic function of the liver.

In this study, administration of CCl_4 (1.5 ml/kg b.wt. i/p) developed a significant elevation of serum total, direct and indirect bilirubin when compared to control animals, this increase due to an inadequacy in excretion of bile by the hepatic cells which lead to increased level of bile in serum. Likewise, silymarin, water and ethanol extracts of fig exhibited a marked decrease in the aforementioned parameters in comparison to CCl_4 treated rats, this confirm the possibility of this herb to stabilize biliary dysfunction of liver of rats during harmful effects occurred from CCl_4. Our results reinforced by those of ***Krishna et al., (2007****)* in which the methanol extract of the of *Ficus carica* at an oral dose of 500 mg/kg in rats with liver damage induced by carbon tetrachloride showed lowering the levels of serum total bilirubin.

In this study, administration of CCl_4 developed a significant elevation of serum MDA alongside a marked reduction in antioxidant enzymes in comparison to untreated group. The water and methanol extract of the of *Ficus carica* at an oral dose of 400 mg/kg in rats with liver damage induced by carbon tetrachloride showed lowering the levels MDA, elevated the reduced levels of liver cytosolic SOD, catalase, and reduced glutathione activity. These antioxidant enzymes are mixed up in the reduction of ROS and peroxides produced in the living organisms, thus play a mandatory role in the maintenance of the redox status to take everything into account ***(Mahmud et al., 2012).***

Our data were supported by those of ***Krishna et al., (2007),*** the methanol extract of the of *Ficus carica* in rats with liver malfunction induced by carbon tetrachloride showed significant decrease in serum malondialdehyde (MDA) equivalent an index of lipid peroxidation of the liver.

These results were in agreement with ***Mongi and Abdelfattah (2012),*** the authors found hepatic antioxidant scavenging capacity, were significantly improved following administration of *Ficus carica* stem extract in methanol-created hepatotoxicity in male Wistar rats. Concerning the histopathological findings, administration of CCl_4 induced many changes in the liver histological picture of rats include markedly dilated central vein filled with red blood cells surrounded by cords and rows of hepatocytes and massive area of fatty changes of the liver cell with increased vacuolated cytoplasm and aggregation of inflammatory cells. Similar findings were observed by ***Aghel et al., (2011),*** the CCl_4 induced group (0.2 mL/kg in olive oil orally), showed severe hepatotoxicity, massive fatty changes, necrosis, ballooning, degeneration and broad infiltration of the lymphocytes and Kupffer cells around the central vein. Also the same findings presented by ***Adeneye et al., (2009)*** in there study, 1.5 mL/kg CCl_4 in 20% in olive oil treated rats, liver sections showing severely congested hepatic central vein and fat globules spread around with deposits in hepatic cells indicating fatty hepatic degeneration.

Oral administration of water extract of fig 400mg/kg b.wt. 3 times a week for 9 weeks reduced the histopathological lesions caused by CCl_4 and showed moderate congestion of the central vein with few

aggregation of inflammatory cells surrounded by normal hepatocytes. In the ether fig extract, liver sections revealed mild congestion of the central vein and mild fatty changes of the hepatocytes.

Our findings were in agreement with ***Krishna et al., (2007),*** who found that the liver sections of the rats administered methanol extract of *Ficus carica* with an oral dose of 500 mg/kg followed by CCl_4 intoxication exhibited a signs of protection as it was apparent by the absence of necrosis and vacuoles. ***Aghel et al. (2011)*** observed similar results, the histological picture of liver sections of mice treated with ethanol *Ficus carica* extract 200 mg/kg orally showed normal lobular pattern with a mild degree of fatty changes, necrosis and lymphocytic infiltration almost comparable to the normal control group.

Adeneye et al., (2009) found the same results that rat liver pretreated with aqueous extract of *Ficus* for 7 days before induction of hepatotoxicity with CCl_4 revealing mildly congested hepatic central vein, mild bile ductal proliferation, and normal hepatocytes .

These results of biochemical parameters, antioxidant activities and histopathological examinations were compared to the standard hepatoprotective drug, silymarin (25 mg/kg b.wt.) with CCl_4 (1.5 ml/kg b.wt. I.P.) The water and ether extracts of fig were found to possess a similar hepatoprotective potentials. ***Visweswaram et al., (1988)*** had used silymarin for hepatotoxicity caused by carbon tetrachloride and found it to be hepatoprotective agent.

The present study showed that a 400 mg/kg WEF and EEF dose has beneficial effects in decreasing the elevated serum AST, ALT, ALP, GGT, total bilirubin and liver levels of MDA, and increased albumin, total proteins, GSH, CAT, and SOD activities in hepatotoxic rats. Histological analyses of the liver indicated that the extracts reduced the damage as compared to the carbon tetrachloride group. The precautionary effects of *Ficus carica* on histopathological and biochemical parameters of liver tissues in lesions of CCL4-induced hepatotoxicity in rats had not previously been reported. This study showed that *Ficus carica* might prevent CCL4-induced hepatotoxicity and the related oxidative stress by inhibiting free radical generation and by restoration of the antioxidant activities.

Conclusion

Summing up our observations, *Ficus carica* fruits, either water or ether extracts reinstate the integrity of hepatic cells and decreases the oxidative stress and lipid peroxidation; restores the antioxidant activities and keep the protein synthetic function of the liver. That herb seems to be an interesting treatment of liver disorders and can be used in the pharmaceutical industry.

REFERENCES

1. Abdel Aziz A.D., Sayed A.A., Ahmed A.H. and Salim D.M. (2014): The ameliorative effect of L-carnitine on experimentally induced liver cirrhosis in male albino rats. J. Amer. Sci. 10 (11): 8-18.
2. Adeneye A.A., Olagunju J.A., Banjo A.A.F., Abdul S.F., Sanusi O.A., Sanni O.O, Osarodion B.A. and Shonoiki O.E. (2009): The aqueous seed extract of Carica papaya linn. prevents carbon tetrachloride induced hepatotoxicity in rats. International Journal of Applied Research in Natural Products Vol. (2) No(2).
3. Aebi H. (1974): Catalase, In: Bergmeryer H.U. and Ulrich H. "Methods of Enzymatic Analysis" 2nd ed., Verlag: Chemic, Weinhein, New York, Pp: 673.
4. Aghel N., Kalantari H. and Rezazadeh S. (2011): Hepatoprotective effect of Ficus carica leaf extract on mice intoxicated with carbon tetrachloride. Iranian Journal of Pharmaceutical research (IJPR) 10(1):63-8.
5. Althnaian T., Albokhadaim I. and El Bahr S.M. (2013): Biochemical and histopathological study in rats intoxicated with carbon tetrachloride and treated with camel milk. Springer plus. 2(57) doi: 10.1186/2193-1801.
6. Aref H.L., Salah K.B., Chaumont J.P., Fekih A., Aouni M. and Said K. (2010): In-vitro antimicrobial activity of four Ficus carica latex fractions against resistant human pathogens (antimicrobial activity of Ficus carica latex). Pak. J. Pharm. Sci. 23: 53-58.
7. Bahlooli S., Mohebipoor A., Mohammedi S., Kohhnavard M. and Pashapoo S. (2007): Comparative study of fig tree efficacy in the treatment of common warts (Verruca vulgaris) vs. cryotherapy. Int. J. Dermatol. 46: 524-526.
8. Bancroft J.D. and Stevens A. (1996): Theory and Practical of Histological Techniques, 3rd Ed. Churchill Livingstone, New York.
9. Belfield A. and Goldberg D.M. (1971): Revised assay for serum phenyl phosphate activity using 4 amino antipyrine enzymes. 12:561-573.
10. Clawson G.A. (1989): Mechanism of carbon tetrachloride hepatotoxicity. Pathol. Immunopathol. Res. 8: 104-112.
11. Culling C.F. (1974): Hand Book of Histopathological and Histochemical Techniques.3rd Ed. Butter Worth, London, Boston.
12. Doumas B.T. and Biggs H.G., (1976): Standard Methods of Clinical Chemistry, Academic Press N.Y.7 (175).
13. Drouliscos N.J., Macris B. J., and Kokke R.(1976): Growth of Fusarium moniliforme on carob aqueous extract and nutritional evaluation of its biomass. Appl. Environ. Microbiol. 31(5): 691–694.
14. Gond N.Y. andKhadabadi S.S. (2008): hepatoprotective activity of Ficus carica leaf extract on rifampicin-induced hepatic damage in rats. Ind. J. Pharm. Sci. 70: 364-366.
15. Henry R.J. (1964): Clinical Chemistry, Harper & Row Publishers. New York, P: 181.
16. Hewitt M., Enoch S.J., Madden J.C., Przybylak K.R. and Cronin M.T. (2013): Hepatotoxicity: a scheme for generating chemical categories for read-across, structural alerts and insights into mechanism(s) of action. Crit. Rev. Toxicol. 43(7):537-58.
17. Hukkeri V.I., Jaiprakash B., Lavhale M.S., Karadi R.V and Kuppast I.J. (2002): Hepatoprotective activity of Anthus excels roxb leave extracts on experimental liver damage in rats. J. Pharmacogn. 11:120-128.
18. Jowari S.A., Sabah A.A and Yousif W.H.(2011): Effect of aqueous extraction of Ficus carica fruits on some hematological parameters in female rabbits. Baghdad science journal .8(1)59-65.
19. Kanter M., Meral I., Dede S., Cemek M., Ozbek H., Uygan I. and Gunduz H. (2003): Effects of Nigella sativa L. and Urtica dioica L. on lipid peroxidation, antioxidant enzyme systems and some liver enzymes in CCl4 treated rats. Journal of Veterinary Medicine. 50: 264–268.
20. Kaplan, L.A.; Pesce, A.J. (1992): Clinical Chemistry, 2nd Ed., St. Louis, C.V. Mosby Company.
21. Khan A.A. and Alzohairy M. (2011): Hepatoprotective effects of camel milk against CCl4-induced hepatotoxicity in Rats. Asian J. Biochem. 6(2):171–180.
22. Khodeary M.F, Abeer A. I., Shereen M. S., Atef A. F and Essam M., (2009): Potential ameliorative role of silymarin against methyl parathion induced oxidative stress and hepato-renal toxicity in albino rats. Mansoura J. Forensic Med. Clin. Toxicol 17 (1):15-39.
23. Krishna M. G., Pallavi E., Ravi Kumar B., Ramesh M. and Venkatesh S. (2007): Hepatoprotective activity of Ficus carica Linn. leaf extract against carbon tetrachloride induced hepatotoxicity in rats. DARU 15(3): 162-166.
24. Kumar A. (2012): A review on hepatoprotective herbal drugs. International Journal of research in pharmacy and chemistry. 2(1): 2231-2781.
25. Lazreg A.H., Gaaliche B., Fekih A., Mars M., Aouni M., and Pierre J. (2011): In-vivo Cytotoxic and antiviral activities of Ficus carica latex extracts. Nat. Prod. Res. 25: 310-319.
26. Mahmud Z.A., Bachar S.C. and Qais N. (2012): Antioxidant and hepatoprotective activities of ethanolic extracts of leaves of Premna esculenta Roxb. against carbon tetrachloride-induced liver damage in rats. J. Young. Pharm. 4(4): 228–234.
27. McCord J.M. and Fridovich I. (1969): Superoxide dismutase. An enzymatic function for erythrocuprein (hemocuprein). J. Biol. Chem. 244 (22): 6049-6055.
28. Mitra S.K., Seshadri S.J., Venkataranganna M.V., Gopumadhaven S., Venkatesh U.U. and Sarma D.N.K.(2000): Effect of HD-03, an herbal formulation in galactosamine induced hepatopathy in rats. Indian J. Physiol. Pharmacol. 44: 82-86.
29. Mongi S. and Abdelfattah E. (2012): Protective Role of Ficus carica stem extract against hepatic oxidative damage induced by methanol in male Wistar rats. Evidence-Based Complementary and Alternative Medicine. Volume 2012, Article ID 150458, 8 pages, doi:10.1155/2012/150458
30. Moslen M.T., Klaassen C.D., Amdur M.O. and Doull H., (1996): Casarett and Doull's Toxicology the Basic Science of Poisons. 5th ed., McGraw Hill, NY. Pp: 403-416.
31. Nielsen F., Mikkelsen B.B., Nielsen J.B., Andersen H.R. and Grandjean P. (1997): Plasma malondialdehyde as biomarker for oxidative stress. Reference interval and effects of life style factors. Clin .Chem. 43(7):1209-1214.
32. Oliveira A.P., Silva L.R., Ferreres F., Guedes de Pinho P., Valentao P., Silva B.M., Perera J.A. and Andrade P.B. (2010): Chemical assessment and in-vitro and antioxidant capacity of Ficus carica latex. J. Agr. Food Chem. 58: 3393-3398.
33. Orhan I.E., Ustun O. and Sener B. (2011): Estimation of cholinesterase inhibitory and antioxidant effects of the leaf extracts of Anatolian Ficus carica var. domestica and their total phenol and flavonoid contents. Nat. Prod. Commun. 6: 375-378.
34. Palaniyppan V., Bommireddy E. and Hephzibah P. (2013): In-vivo fertility enhancing activity of Ficus carica fruits on male Wister rats. Int. J. Pharmacy Pharm. Sci. 5 (2): 1457-1491.
35. Patil V.V. and Vijay R. P. (2011): Ficus carica Linn.-An Overview. Research Journal of Medicinal Plant, 5: 246-253.
36. Perez C., Canal J.R., Campillo J.E., Romero A. and Torres M.D. (1999): Hypotriglyceridaemic activity of Ficus carica leaves in experimental hypertriglyceridaemic rats. Phytother. Res. 13: 188-191.
37. Podolosky D. K. and Isselbacher K. J. (1991): Cirrhosis in liver. In: Wilson J. D., Braunwald E., Isselbacher K. J., Petersdorf R. G. and Martin J. B. (2nd ed) P: 73-76. Harrison Principle of Internal Medicine. McGraw-Hill, New York.
38. Rajesh M.G. and Latha M.S. (2004): Preliminary evaluation of the antihepatotoxic activity of Kamilari, a polyherbal formulation. J. Ethnopharmacol. 91: 99-104.
39. Richter G., Schwarz H.P., Dorner F. and Turecek P.L. (2002): Activation and inactivation of human factor X by proteases derived from Ficus carica. Brit. J. Haematol. 119: 1042-1051.
40. Roy S.D, Das S., Shil D. and Dutta K.N.(2012): Herbal hepatoprotective agents World Journal of Pharma¬ceutical research. 1, (2), 87-99.
41. Rubnov S., Kashman Y., Rabinowitz R., Schlesinger M. and Mechoulam R. (2001): Suppressors of cancer cell proliferation from fig (Ficus carica) resin: Isolation and structure elucidation. J. Nat. Prod. 64: 993-996.
42. Sedlak J. and Lindsay R.H. (1968): Estimation of total protein-bound and nonprotein sulfhydryl groups in tissue with Ellman reagent. Analytical Biochemistry, 25:192-205.
43. Shih C.C., Wub Y.W. and Linb W.C. (2005): Aqueous extract of Anoectochilus formosanus attenuate hepatic fibrosis induced by carbon tetrachloride in rats. Phytomedicine, 12: 453-460.
44. Souli A., Sebai H., Chehimi L., Rtibi K., Tounsi H., Boubaker S., Sakly M., El Benna J. and Amri M.(2013): Hepatoprotective effect of carob against acute ethanol-induced oxidative stress in rats. Toxicol Ind Health. at PubMed. PMID:23363576.
45. Tietz N.W. (1967): Fundamentals of clinical chemistry W.B. Saunders CO, Philadelphia.
46. Walters M.I and Gerarde H.W. (1970): An ultramicro method for the determination of conjugated and total bilirubin in serum or plasma. Michrochem J: 15:231-243.