# Hepatoprotective Effect of *Anethum Graveolens* Against Paracetamol Induced Hepatotoxicity In Rabbits

**Sameh M El Nabtity, Mohamed A Hashem* and Magda El sayed B Diab****
Depts. of Pharmacology, Clinical Pathology* Faculty of Vet. Medicine and Dept. of Internal Medicine Faculty of Medicine**, Zagazig University.

## ABSTRACT

The present study was conducted to evaluate the hepatoprotective effect of water extract of *Anethum graveolens* seeds (WEAGs) against paracetamol (PCM) induced hepatotoxicity in rabbits using silymarin as a standard hepatoprotective drug.

Twenty four male New Zealand rabbits weighing. 1.5 -2 Kg were classified into four equal groups each of six. The first group (gp1) was kept as a control, the second group (gp2) was received distilled water for four weeks followed by PCM at a dose of 2 g / kg b.wt. orally for 7 successive days. The third group (gp3) : Received WEAGs at a dose of 200 mg/kg b.wt. orally for four weeks followed by PCM by the same previous doses and forth group (gp4): received silymarin at a dose of 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM by the same doses and periods.

The obtained results clearly demonstrated that WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks evoked a significant hepatoprotective, effect against PCM induced hepatotoxicity in rabbits. Which is confirmed by liver function tests, α fetoprotein, lipid profile liver antioxidant enzymes (Catalase and Supreroxide dismutase) and histopathological studies. Yet this clear hepatoprotective effect is still less than that of silymarin at the doses used in this study.

## INTRODUCTION

Liver diseases are considered one of the serious health problems. Steroids, vaccines and antiviral drugs that are employed as therapeutic agents for liver diseases have potential adverse effects especially when administered for long periods *(1)*.

There is a worldwide trend for the use of traditional herbal drugs for the treatment of liver diseases. Several leads from plant sources have been found as potential hepatoprotective agents with diverse chemical structures. Although a big list of hepatoprotective phytomolecules are reported in the scientific literature, only few were potent against various types of liver damages *(2)*.

*Anethum graveolens* L (Umbilliferae) known as dill, is an annual herb growing in the Mediterranean region, Europe, central and southern Asia. Also it is widely cultured in southeastern region of Iran. The plant is used both medicinally and as an aromatic herb, spice and cookery. *Anethum graveolens* has been used traditionally for gastrointestinal aliment such as flatulence, indigestion, stomachache colic and to tract intestinal gas *(3)*. The presence of flavonoids, phenolic compounds and essential oil in *Anethum graveolens* has been reported *(4-7)*.

Some pharmacological actions of dill such as antimicrobial *(8)* antispasmodic *(9)* antisecretory and mucosal protective effect *(3)* and anti-hypercholesterolemic activities of the crude extract have previously been reported *(10)*.

The present study was designed to evaluate the hepatoprotective effect of water extract of *Anethum graveolens* seeds (WEAGs) against paracetamol induced hepatic damage in rabbits using silymarin as a standard drug with special reference to its effects on lipid profile.

## MATERIAL AND METHODS

### Material

### I. Experimental animals

Twenty four male New Zealand rabbits weighing 1.5 – 2 Kg were used in this study.

They were obtained from San El Hagar rabbit Farms. All rabbits were kept under observation and acclimatization periods of 7 days to the laboratory enviroment before starting the experiment. Animals were fed standard rabbit pellets and watered *ad libitum* all over the experiment time, They were housed in battery system in good hygienic conditions.

**II. Plant materials**

Anethum graveolens seeds were collected from local markets, identified by department of Pharmacognosy, Faculty of Pharmacy, Zagazig University.

**III. Silymarin (Legalon 140 )®**

Was used as a standard hepatoprotective drug. It was obtained from(CID-Giza,Egypt.)

**IV. Paracetamol** tablets 500 mg (cetal) ®.It was obtained from Eipico Tenth of Ramadan Egypt.

**Methods**

**Preparation of water extract of *Anethum graveolens* seeds extract**

One Kg of *Anethum grareolens* seeds was air-dried away from sun then pulverized. The powder was soaked in adequate amount of distilled water for one week then filtered. The plant was soaked again in adequate amount of water for 48 hours then filtered again (two sequences times).

The filtrate was stored in clean dry container and lyophilized by using freeze drier, model SB4 England Hem. Lab., England. The lyophilized extract was kept in tightly closed container at 4°C till used *(3)*. N.B The percentage Yeild of WEAGs was found to be 10% .

**Experimental design**

Twenty four male New Zealand rabbits 1.5 – 2 Kg b.wt. were classified into four equal groups each of six as follows:

Group (G1): Control non treated group.

Group (G2): Received D.W. for 4 weeks followed by paracetamol at a dose of 2 g/kg b.wt. orally for one week.

Group (G3): Received (WEAGs) at a dose of 200 mg/kg b.wt. orally for 4 weeks followed by paracetamol at the same dose and period.

Group (G4): Received silymarin at a dose of 6.53 mg/kg b.wt. orally for 4 weeks followed by paracetamol at the same dose and period.

N.B. the dose of WEAGs in this study was chosen based on our preliminary studies.

**Collection of samples**

At the end of the experiment, all animals were fasted for 12 hours then slaughtered and the following samples were collected.

1) Blood in clean glass tubes was allowed to clot and serum was separated by centrifugation at 3000 r.p.m for 10 minutes For determination of liver function test parameters, α feto protein as a tumor marker and lipid profile.

2) Liver tissues : were taken from animals of all groups. Each liver tissue was immediately washed with saline, blotted on filter paper weighted and 1 gm of each sample was homogenized in 10 ml of distilled water using electrical homogenizer, centrifuged at 3000 r.p.m for 15 minutes and the resulted supernatant was collected to be used for estimation of antioxidant enzymes.

3) Liver samples were fixed in 10% neutral buffered formalin for histopathological examination

***Biochemical determinations***

**Liver function testes**

*Serum* Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) *(11)* and Alkaline phosphatase *(12)*. Serum total proteins *(13)*. Serum albumin *(14)*. Serum globulins was calculated as difference between total proteins and albumin. Serum total and

direct bilirubin *(15)* Quantitative determination of serum gamma glutamyl transferase *(16).*

**Tumor marker**

Serum alpha feto-protein *(17)*

**Antioxidant enzymes**

Catalase activity in the liver homogenate *(18)*. Superoxide dismutase activity in the liver homogenate *(19,20)* was determined .

**Lipid profile**

Total cholesterol *(21)* Triglycerides *(22)* serum HDL-cholesterol *(23),*'LDL-Cholesterol: *(24)* and VLDL-cholesterol *(25)*

***3.Histopathological examination of the liver (26)***

***4.Data analysis:*** Data were statistically analysed using the computer program SPSS/pc + *(27)*.

## RESULTS AND DISCUSSION

Complications of liver diseases can be treated and /or prevented using herbal extracts with expectations of a satisfactory outcome. Herbal medicine can prevent the occurrence of chronic liver diseases *(28).*

*Anethum graveolens* has been reported to have a variety of biological effects including antimicrobial, antisecretory, mucosal protective and hypolipidaemic activity *(29).* Literature about hepatoprotective effects of *Anethum graveolens* and the scientific data about these effects is scarce. The present study was designed to evaluate the hepatoprotective effects of WEAGs against paracetamol (PCM) induced hepatotoxicity in rabbits.

Our results Tables 1,2,3 showed that WEAGs elicited a significant hepatoprotective activity against PCM induced hepatotoxicity as evidenced by its ameliorative effect on the levels of AST, ALT, ALP, total proteins, albumin, globulins, T. Bilirubin, direct bilirubin, GGT, and alpha fetoprotein. In addition the antioxidant activities of WEAGs extracts was confirmed by the activity of the antioxidant enzymes (catalase and superoxide dismutase) in liver tissues Table 2. This results are supported by our histopathological changes.

Our results showed that PCM induced significant increase in AST, ALT, T. bilirubin, d. bilirubin, Alkaline phosphates, GGT, α fetoprotein compared to control. Furthermore PCM evoked a significant decrease in antioxidant enzymes (CAT and SOD) activity in liver tissue.

PCM is commonly used as analgesic and antipyretic drug and is safe in therapeutic doses but produces fatal hepatic necrosis with toxic doses *(30).* The toxic effects of PCM is due to oxidative damage induced by its metabolite N-acetyl –p-benzoquinoneimine produced by the action of cytochrome P-450 in the liver. This metabolite reacts with reduced glutathione (GSH) to yield non-toxic 3-GS-Yl-PCM. Depletion of GSH causes the remaining quinone and other natural endogenous oxygen species to bind to cellular macromolecules leading to cell death *(31)*

The present results were supported by those previously obtained *(32).* They reported that PCM-induced toxicity produced significant increase in serum AST, ALT, ALP enzymes which may be attributed to cytochrome P-450 generated metabolites which modify the target proteins.

The alterations in serum ALP level may be attributed to cholestasis *(33).* Concerning the effects of PCM on serum albumin and total proteins, our results showed that PCM evoked significant decrease in serum albumin and total proteins. These results are in the same direction with *Galisteo, et al., (34).* They reported hypoalbuminaemia and hypoproteinaemia in paracetamol induced hepatic damage.

Regarding the effect of PCM on serum total and direct bilirubin in serum our results showed significant increase in both total and direct bilirubin level in PCM intoxicatd group. This indicates hepatocellular damage which lead to hepatocellular jaundice as a result of cholestasis and difficulty in uptake of conjugated bilirubin *(35).* Such result was confirmed histopathologically (Fig.1)

Daily administration of WEAGs at a dose of 200 mg/kg b.wt. (G3) orally for 4 weeks resulted in significant decrease in serum AST, ALT, ALP, total and direct bilirubin and α fetoprotein and significant increase in serum albumin and total proteins compared to PCM treated group (gp 2). This result is in the same line with those obtained by Yazdanparast and Bahramikia ***(29)***. They reported that *Anethum graveolens* extract in rats appears to protect animals against hepatic injury due to high-fat diet as suggested by nearly normal levels of ALT, AST, ALP.

On lipid profile(table 4) WEAGs evoked significant decrease in serum cholesterol, triacylglyceroles, LDL and VLDL, meanwhile it elicited significant increase in HDL in comparison with PCM treated group (G2). Such results are compatible with Hajhashemi and Abbasi, ***(36)*** They reported that *Anethum graveolens* has significant lipid lowering effect and is a promising cardio protective agent. Weggemans and Trautwein, ***(37)*** have reported that flavonoids intake decreased LDL and increased HDL in hypercholesterolemic individuals. Many studies have confirmed the presence of phenolic compounds mainly flavonoids in Anethum graveolens ***(4-7)***. Considering these facts it may be possible that these active principles are responsible for lowering total cholesterol and LDL, triglycerides and elevated HDL in WEAGs treated groups.

The possible underlying mechanism by which WEAGs could exert its lipid lowering activities is not completely elucidated. At the moment,several fundamental mechanisms have been proposed. A decrease in cholesterol absorption from intestine, through binding to bile acids and an increase in faecal bile acids excretion has been considered as mechanism of action ***(29)***. Moreover, *A. graveolens* treated rats showed further decrease in HMG-CoA reductase activity thus suggesting a possible interaction with the enzyme resulting in lower total cholesterol levels.

PCM induced hypercholesterolaemia may be attributed to the unability of liver to convert cholesterol to cholesterol ester. It may be also due to decrease in cholesterol excretion through bile duct as a result of obstruction of bile canaliculi due to hepatic damage ***(38)*** in addition the histopathological results revealed bile duct hyperplasia in PCM treated group (Fig. 2) which may explain this hypercholesterolaemia.

Concerning the effect of WEAGs on the liver antioxidant enzymes CAT and SOD of rabbits treated with PCM, our results Table 5 showed that PCM administration resulted in a significant decrease of activities of liver CAT and SOD enzymes compared to control group. While prophylactic administration of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks elicited a significant increase in these antioxidant enzymes activities in liver tissue homogenate of rabbits. Needless to say these results reinforced those previously obtained ***(39)***. They reported that treatment with different fractions of *A. graveolens* extract (AGE) significantly increased the hepatic antioxidant activities of SOD, CAT and GSH, along with decreased lipid peroxidation in high fat diet (HFD) treated rats. They concluded that AGE besides its hypolipidaemic property, could protect the liver against the HFD-induced oxidative damage in rats.

Our results clearly demonstrated that WEAGs at a dose of 200 mg/kg b.wt. orally has hepatoprotective effect against PCM induced hepatotoxicity which is confirmed by the histopathological findings (Figs 1,2,3,4.) but this effect is still lesser than that of silymarin

**Table 1. Effects of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks on some liver enzymes in PCM induced Hepatotoxicity in rabbits (Mean±S.E) n=6**

| Groups | ALT (µ/L) | AST (µ/L) | Alkaline phosphatase ALP (µ/L) | GGT (µ/L) |
|---|---|---|---|---|
| Control | 3.67± 0.33$^{b}$ | 7.33± 0.33$^{c}$ | 52.67$^{b}$±3.4 | 19.33±0.1.2$^{b}$ |
| PCM 2 g/Kg b.wt. orally for 7 days | 18.67 ± 0.88$^{a}$ | 25.0 ± 1.15$^{a}$ | 102.33$^{a}$±7.2 | 32.33 ± 1.45$^{a}$ |
| WEAGs 200 mg/ kg b.wt. for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 6.0 ± 1.15$^{b}$ | 14 ± 1.0 $^{b}$ | 67.33 ± 6.4$^{b}$ | 24.33 ± 1.45$^{b}$ |
| Silymarin 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 5.33 ± 0.67$^{b}$ | 14 ± 1.0 $^{b}$ | 64.33 ± 4.3 $^{b}$ | 24.33± 1.76$^{b}$ |

Means within the same column carrying different superscripts are significant at ($P < 0.05$)

**Table 2. Effects of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks on serum total proteins, albumin, globulines,A/G ratio and α feto-protein.(Mean±S.E) n=6**

| Groups | S. Total protein g/dl | S. Albumin g/dl | S. Globulins g/dl | A/G Ratio | α feto-proteins ng/ml |
|---|---|---|---|---|---|
| Control | 6.9± 0.33$^{a}$ | 3.87± 0.033$^{a}$ | 3.067±0.033 $^{a}$ | 1.26±0.20$^{a}$ | 1.15±0.29$^{c}$ |
| PCM 2 g/Kg b.wt. orally for 7 days | 6.33± 0.088$^{b}$ | 3.03± 0.033$^{c}$ | 3.30±0.058$^{a}$ | 0.91± 0.015$^{a}$ | 9.33 ± 0.88$^{a}$ |
| WEAgs 200 mg/ kg b.wt. for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 6.83± 0.088$^{a}$ | 3.53 ± .066 | 3.30 ± .058$^{a}$ | 1.07± 0.029$^{b}$ | 3.7 ± 0.5$^{b}$ |
| Silymarin 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 6.80 ± 0.15$^{a}$ | 3.50 ± 0.58 | 3.30 ± 0.21 $^{a}$ | 1.073± 0.089$^{b}$ | 3.30± 0.35$^{b}$ |

Means within the same column carrying different superscripts are significant at ($P < 0.05$)

**Table 3. Effects of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks on total direct and indirect bilirubin (Mean±S.E) n=6**

| Groups | Total bilirubin mg/dl | Direct bilirubin mg/dl | Indirect bilirubin mg/dl |
|---|---|---|---|
| Control | 0.56± 0.02 $^{b}$ | 0.127± 0.013 $^{b}$ | 0.43 ± 0.018 $^{b}$ |
| PCM 2 g/Kg b.wt. orally for 7 days | 0.88 ± 0.49 $^{a}$ | 0.33 ± 0.17 $^{a}$ | 0.55± 0.037 $^{a}$ |
| WEAgs 200 mg/ kg b.wt. for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 0.57 ± 0.02 $^{b}$ | 0.127 ± 0.013 $^{b}$ | 0.45 ± 0.007 $^{b}$ |
| Silymarin 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 0.58 ± 0.02 $^{b}$ | 0.127 ± 0.013 $^{b}$ | 0.46 ± 0.007 $^{b}$ |

Means within the same column carrying different superscripts are significant at ($P < 0.05$)

**Table 4. Effects of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks on serum lipid profile . (Mean±S.E) n=6**

| Groups | S. Cholesterol. mg/dl | Triglycerides mg/dl | HDL mg/dl | LDL mg/dl | VLDL mg/dl |
|---|---|---|---|---|---|
| Control | 69.0 ± 2.65 [b] | 79.0 ± 0.58 [b] | 39.33 ±0.33 [a] | 13.87 ±2.54 [b] | 15.8 ±0.12 [b] |
| PCM 2 g/Kg b.wt. orally for 7 days | 128.33 ±5.2 [a] | 115.33 ± 6.36 [a] | 32.00 ±0.58 [b] | 73.27 ± 3.9 [a] | 23.06 ± 1.27 [a] |
| WEAgs 200 mg/ kg b.wt. for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 81.0 ± 4.36 [b] | 77.0 ± 9.6 [b] | 38.0 ± 0.58 [a] | 28.06 ± 6.29 [b] | 15.4 ± 1.92 [b] |
| Silymarin 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 80.67 ± 3.48 [b] | 75.67 ± 3.18 [b] | 38.33 ± 0.33 [a] | 27.20 ± 3.49 [b] | 15.13 ± 0.64 [b] |

Means within the same column carrying different superscripts are significant at ($P < 0.05$)

**Table 5. Effects of WEAGs at a dose of 200 mg/kg b.wt. orally for 4 weeks on the activity of liver antioxidant enzymes (catalase and superoxide dismutase) (eu/mg protein) (Mean±S.E) n=6**

| Groups | Hepatic catalase | Hepatic superoxide dismutase |
|---|---|---|
| Control | 22.58± 0.55 [a] | 28.5± 0.60 [a] |
| PCM 2 g/Kg b.wt. orally for 7 days | 12.23 ± 0.33 [a] | 13.53 ± 0.42 [b] |
| WEAgs 200 mg/ kg b.wt. for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 20.14 ± 0.72 [a] | 24.61 ± 0.81 [a] |
| Silymarin 6.53 mg/kg b.wt. orally for 4 weeks followed by PCM 2 g/kg b.wt. orally for 7 days | 20.17 ± 0.83 [a] | 25.71 ± 0.85 [a] |

Means within the same column carrying different superscripts are significant at ($P < 0.05$)

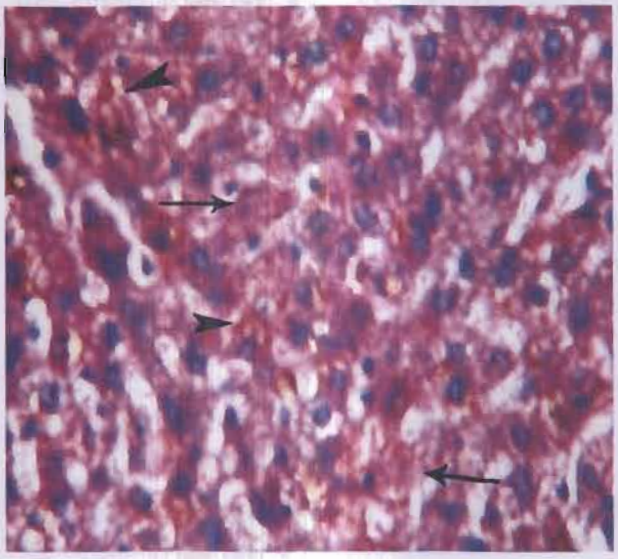

**Fig. 1.** Photomicrograph of the liver section of rabbits administered PCM at a dose of 2 gm/kg.b.wt. orally for 7 successive days, showing coagulative necrosis and cholestasis (Arrow head)(H&E, X 1200).

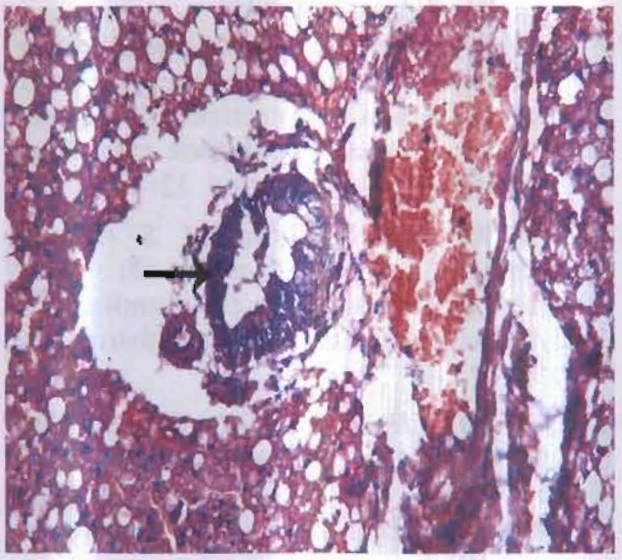

**Fig. 2.** Photomicrograph of the liver section of rabbits administered PCM at a dose of 2 gm/kg.b.wt. orally for 7 successive days, showed portal area with edema, congested blood vessels and hyperplasia of lining epithelium of bile duct, beside fatty changes in the adjacent hepatocytes (H&E X 1200)

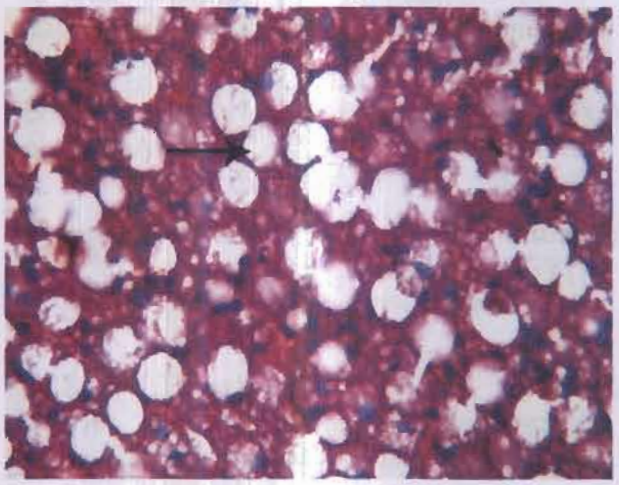

**Fig. 3.** Photomicrograph of the liver section of rabbits administered WEAgs at a dose of 200 gm/kg.b.wt. orally for 4 weeks followed by PCM (2 gm/kg b.wt.) orally for 7 days showed moderate fatty changes Arrow.(H&E X 300.)

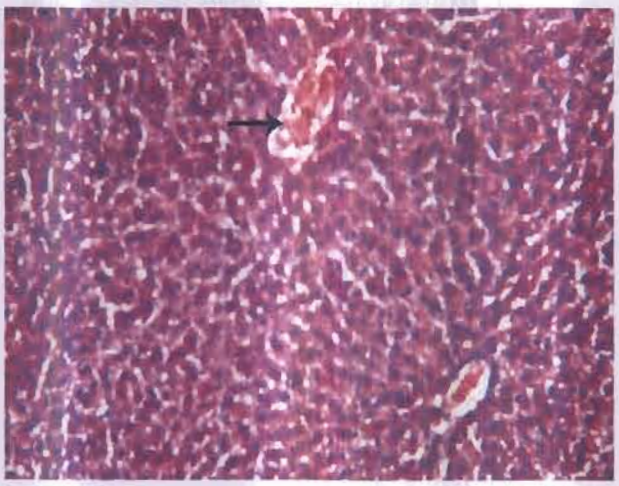

**Fig. 4.** Photomicrograph of the liver section of rabbits administered silymarin 6.53 gm/kg.b.wt. orally for 7 days showed mild congestion in hepatic blood vessels. Arrow.(H&E X 300.)

## REFERENCES


1. ***Sehrawat A, Khan A, Prasad L and Sultana S (2006):*** Butea monosperma and chemomodulation : protective role against thioacetamide- mediated hepatic alterations in Wistar rats. Phytomedicine 13: 157-62.

2. ***Rajesh M G and Latha M S (2004):*** Preliminary evaluation of the antihepatotoxic activity of Kamilari, a polyherbal formulation. J Ethnopharmacol. 91: 99-103.

3. ***Hosseinzadeh H, Karimi GR and Ameri M (2002):*** Effects of *Anethum graveolens* L. seed extracts on experimental gastric irritation models in mice. BMC Pharmacol 2: 1–5

4. ***Charles D J, Simon J E and Widerlechner M P(1995):*** Characterization of essential oil of dill (*Anethum graveolens*). J Essen Oil Res; 7: 11–20.

5. ***Ishikawa T, Kudo M and Kitajima J (2002):*** Water-soluble constituents of Dill. Chem Pharm Bull 50:501–507.

6. ***Justesen U and Knuthsen P (2001):*** Composition of flavonoids in fresh herbs and calculation of flavonoid intake by use of herbs in traditional Danish dishes. Food Chem 73:245–250.

7. ***Vera RR and Chane-Ming J (1998):*** Chemical Composition of essential oil of dill (*Anethum graveolens* L.) growing in Reunion. J Essen Oil Res 10:539–542.

8. ***Chaurasia SC and Jain PC (1978):*** Antibacterial activity of essential oils of four medicinal plants. Indian J Hosp Pharm 15:166–168.

9. ***Fleming T (2000):*** PDR for Herbal Medicines. New Jersy: Medical Economics Company: 252–253.

10. ***Yazdanparast R and Alavi M (2001):*** Antihyperlipidaemic and antihypercholesterolaemic effects of *Anethum graveolens* leaves after the removal of furocoumarins. Cytobios 105:185–191

11. ***Tietz N W (1976):*** Fundamentals of Clinical Chemistry W.B.Saunders Co. Philadelphia.

12. ***Belfield A and Goldberg D M (1971):*** Revised assay for serum phenyl phosphate activity using 4-amino-antipyrine-Enzyme, 12 : 561- 573.

13. ***Henry R J (1964):*** Clinical Chemistry, Harper & Row publishers. New York P: 181.

14. ***Doumas,B T and Biggs, H G (1976):*** Standard Methods of Clinical Chemistry Academic Press N.Y.7 (175).

15. ***Monnet L (1963):***Determination of bilirubin . Annual Biol.Clin.,21;717.

16. ***Szaz G (1969):*** Quantitative determination of gamma glutamyl transferase in serum or plasma. Clin. Chem.. 22: 124-136.

17. ***Batzer F R (1980):*** Forty assay of α fetoprotein as a predisposing cause of cancer in liver. J. Clinical Endocrinology and Metabolic Disorders, 34(1): 1-3.

18. ***Sinha A K (1972):*** Colorimetric assay of catalase. Analytical Biochemistry 47: 389.

19. ***Misra H P and Fridovich I (1972):*** Role of superoxide anion in autooxidation of epinephrine simple assay for SOD. J.Biochem.; 247-317.

20. ***Packer,L and Glazer, AN (1990):*** Method in Enzymology. Vol.186. Part.B Academic Press Inc.New York Pp. 251.

21. ***Allain, C C; Flegg H M and Richmond W (1974):*** Enzymatic determination of total serum cholesterol. Clin. Chem., 20, 470-475

22. ***Fossati P and Prencipe L (1982):*** Enzymatic determination of serum triglycerides. Clin. Chem., 28, 2077 .

23. ***Burstein, M. (1970):*** Determination of lipoproteins HDL-cholesterol. Lipid Res. 11, 583.

24. ***Assmann G , Jabs HU , Kohnret U , Nolte W and Schriewer H (1984):*** LDL-

cholesterol determination. Clin. Chim. Acta., 140. 77-83

***25.Neal-Pinckney (2004):*** VLDL-cholesterol calculation. User-1166 Sll. Cable Mindspring .Com 15-5

***26.Bancroft, J; Stevens A and Turner, D (1996):*** Theory and Practice of Histological Techniques, 3rd Ed. Churchill Livingstone,New York.

***27.SPSS Win.(1995):*** Statistical Program Under Windows, U.S.A.

***28.Hsu L M ; Huang Y S ; Chang F Y and Lee S D (2006):*** Acute hepatitis induced by hepatoprotective herb xiao-chai-hu-tang. J.Chin. Med. Assoc. 69(2):86-88.

***29.Yazdanparast R and Bahramikia S (2008)*** Evaluation of the effect of *Anethum graveolens* L. crude extracts on serum lipids and lipoproteins profiles in hypercholesterolaemic rats DARU Vol. 16, No. 2

***30.Mitchell JR, Jollow DJ, Potter WZ, Gillettee JR, and Brodie BN (1973):*** Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther. 187: 185-88.

***31.Udem SC, Madubunyy I, Okoye JOA, and Anika SM. (1997):*** Anti-hepatotoxic effects of the ethanolic extracts of Combretum dolichopetalum root bark and Morinda lucida leaf. Fitoterapia.; 68: 21-26.

***32.Gripioti A D, Theocharis SE, Papadimas GK, Demopouls CA, Papadopoulou DZ, Basayiannis AC and Mykoniatis MG (2005):*** Platelet-activating factor (PAF) involvement in acetaminophen-induced liver toxicity and regeneration. Arch. Toxicol. Epub. Ahead of Print.

***33.Coles E H (1986):*** Veterinary Clinical Pathology. 4th Ed. W.P. Saunders Company. Philadelphia, London, Toronto.

***34.Galisteo, M; Suarez, R; Del, P; Montilla, M; Del, U; Jimenez, J Gil, A; Fans, M.J. and Navarro, M (2000):*** Antihepatotoxic activity of Rosmarimus tomentosus in a model of acute hepatic damage induced by thioacetamide phytother. Res., 14(7): 522-526.

***35. Mandal S C, Saraswthi B, Kuma CK, Mohana LS and Maiti BC (2000):*** Protective effect of leaf extract of ficus hispida against paracetamol induced hepatotoxicity in rats. Phytother. Res., 14(6): 457-459.

***36.Hajhashemi V and Abdasi N (2008):*** hypolipidimic activity of anethum graveolens in rats. Phytother. Res. Mar., 22(3): 372-5.25.

***37.Weggemans RM, and Trautwein EA. (2003):*** Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a Meta analysis. Eur J Clin Nutr 57:940–946.

***38.Kim, SN; Kim, SY; Yim, HK; Lee, WY; Ham, KS; Kim, SK; Yoon, M Y and Kim, YC (1999):*** Effect of dimethyle -4, 4-dimethoxy -5, 6, 6-dimehylenedi – oxybiphynyl -2,2-dicarboxylate (DDB) on chemical –induced liver injury. Biol. Pharm. Bull., 22(1): 93-95.

***39.Bahramikia S and Yazdanparast, R (2009):*** Efficacy of different fractions of Anethum graveolens leaves on serum lipoproteins and serum and liver oxidative status in experimentally induced hypercholesterolaemic rat models. Am. J. Clin. Med. 37(4):685-99.12.

## الملخص العربى

### التأثير الواقى للكبد لخلاصة بذور الشبت المائية ضد التسمم الكبدى المحدث بالباراسيتامول فى الأرانب

**سامح محمد مصطفىالنبتيتى ، محمد عبد العظيم هاشم * ، وماجدة السيد بدر دياب****
قسم الفارماكولوجيا- قسم الباثولوجيا الإكلينيكية*كلية الطب البيطرى - جامعة الزقازيق
قسم الأمراض الباطنة العامة كلية الطب** - جامعة الزقازيق

تعد أمراض الكبد من أكثر المشاكل الصحية إنتشارا فى هذه الأيام . كما أن دواء الباراسيتامول يعد من أكثر الأدوية شيوعا واستخداما كمسكن للآلام وخافض للحرارة نظرا لأمانه بالجرعات العلاجية العادية . ولكنه عند الاستخدام بجرعات عالية أوبصورة مفرطة يؤدى إلى تأثيرات ضارة على الكبد وحيث أن هناك إتجاها حديثاً للعودة للمنتجات الطبيعية والعشبية بدلاً من المنتجات الكيميائية وأعراضها الجانبية.

لذا إستهدفت هذه الدراسة التأثير الواقى للكبد لخلاصة بذور الشبت المائية ضد التسمم الكبدى المحدث بالجرعات العالية من الباراسيتامول فى الارانب كمثال لحيونات التجارب .

استخدم فى هذا البحث عدد ٢٤ من ذكور الأرانب النيوزيلاندى البيضاء زنة كل واحد من ١,٥ الى ٢ كجم قسمت إلى أربعة مجموعات متساوية كل واحدة تحتوى على ٦ أرانب.

١ ) المجموعة الأولى تركت كمجموعة ضابطة.

٢ ) المجموعة الثانية أخذت ماء مقطر لمدة أربعة أسابيع ثم باراسيتامول بجرعة ٢ جم/ كجم وزن حى عن طريق الفم لمدة ٧ أيام .

٣ ) المجموعة الثالثة ثم إعطاؤها الخلاصة المائية لبذور الشبت بجرعة ٢٠٠ مجم/ كجم وزن حى عن طريق الفم لمدة ٤ أسابيع ثم بعد ذلك ثم إعطاؤها باراسيتامول بنفس الجرعة و لمده ٧ أيام.

٤ ) المجموعة الرابعة ثم إعطاؤها سليمارين بجرعة ٦,٥٣ مجم/كجم وزن حى عن طريق الفم لمدة ٤ أسابيع ثم الباراسيتامول بنفس الجرعات والمدة السابقة.

وبعد ذلك ثم أخذ عينات دم بعد ذبح جميع الأرانب وعمل وظائف كبد كاملة وتشمل GGT, AST , ALT وصفراء مباشرة وكلية وغير مباشرة وكذلك فوسفاتيز قاعدى كما تم قياس نسبة البروتينات الكلية والزلال فى الدم وحساب نسبة جلبيولين الدم . وكذلك صورة دهون كاملة بالدم كما تم قياس نسبة الألفافيتوبروتين كأحد أهم دلالات الأورام الخاصة بالكبد كما تم قياس نشاط الانزيمات المضادة للأكسدة فى نسيج الكبد مثل إنزيمى الكتاليز والسوبرأوكسيد ديسميوتيز وكذلك عمل تحاليل باثولوجية لأنسجة الكبد لجميع المجموعات .

**ونستخلص من هذه الدراسة:**

أن الخلاصة المائية لبذور الشبت بجرعة ٢٠٠ مجم/ كجم وزن حى عن طريق الفم لمدة ٤ أسابيع قد نجحت فى وقاية الكبد ضد التسمم الكبدى المحدث بالباراسيتامول بجرعة ٢ جم/كجم وزن حى عن طريق الفم وقد ثبت ذلك عن طريق التحاليل الكيميائية الخاصة بوظائف الكبد وصورة الدهون الكاملة ودلالات الأورام كما أثبتت نتائج تحاليل مضادات الأكسدة فى أنسجة الكبد والتحاليل الباثولوجية قدرة هذه الخلاصة على منع التأكسد الدهنى والتأثير المضاد للأكسدة ولكن مازال تأثيرها بهذه الجرعة أقل من تأثير السليمارين.