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308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
Mob: +92 300 3008585, Fax: +92 41 8815544
E-mail: editorpjn@gmail.com

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Hepatoprotective Effect of Dill (*Anethum graveolens* L.) and Fennel (*Foeniculum vulgare*) Oil on Hepatotoxic Rats

Naeem M. Rabeh and Alaa O. Aboraya
Department of Nutrition and Food Science, Faculty of Home Economics, Helwan University, Cairo, Egypt

Abstract: The present study was carried out to determine the hepatoprotective effect of some herbal oils as Dill (*Anethum graveolens* L.) and Fennel (*foeniculum vulgare*) oil seeds against carbon tetrachloride (CCL_4) that caused hepatotoxicity in rats. The experiment was performed on 30 adult rat that classified into two main groups, the first main group (6 rats) was kept as control (-ve) group while the second main groups (24 rat) were administered a dose of (2 mL CCL_4 /kg b.wt.) twice a week for two weeks to induce chronic damage in the liver then classified into four subgroups (six rats each) as follow, one of them (6 rats) was fed on the basal diet and used as a positive control group (+ve), however, the other three subgroups were fed on basal diets and obtained orally dill oil (1 mL/kg), Fennel oil (1 mL/kg), mixture of (0.5 dill and 0.5 mL/kg fennel) oil, respectively for 4 weeks. The hepatotoxicity produced by CCL_4 administration was found to be inhibited by either Dill (*Anethum graveolens* L.) or Fennel *(foeniculum vulgare)* oil or by the mixture of both Dill and Fennel oil with evidence of significant ($p<0.05$) decrease levels of serum AST and ALT and significantly ($p<0.05$) increase the level of serum total protein and albumin. Moreover, Dill and Fennel oil supplementation induced suppression of the increased ALP activity with the concurrent depletion of raised bilirubins suggests the possibility of these oils to have ability to stabilize biliary dysfunction in rat liver during hepatic injury by CCl_4. On the other hand, the increase in MDA level and the decrease activity of SOD enzymes in liver induced by CCl_4 suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanism to prevent formation of excessive free radicals. Treatment with either Dill or Fennel oil and their mixture significantly ($p<0.05$) reverses these changes. Also, the studied oils have hyoplipidemic effects. Hence it is likely that the mechanism of hepatoprotection of either Dill or Fennel oil is due to its antioxidant effect. Dill or Fennel oil and their mixtures have a potent hepatoprotective action against CCL_4 induced liver toxicity in rats. So that, the use of Dill and Fennel oil in food formulations may be beneficial to patients who suffer from liver diseases associated with oxidative stress.

Key words: Dill oil, Fennel oil, hepatoprotective, antioxidant, lipid peroxidation, carbon tetrachloride, rats

INTRODUCTION

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. The liver helps to purify the blood by changing potentially harmful chemicals into harmless ones (MC Quid, 2003; Ozbek *et al*., 2006).

Hepatotoxicity implies chemical-driven liver damage. Chemicals that cause liver injury are called hepatotoxins. CCl_4 is a volatile organic alkyl halogen that is present in the environment largely because of release from manmade sources. High exposure to CCl_4 can cause liver, kidney damages, headaches, dizziness, sleeping, nausea and vomiting (Beartram and Recnagel, 2005).

The liver disorders are one of the world problems. Despite its frequent occurrence, high morbidity and high mortality, its medical management is currently inadequate, so far not yet any therapy has successfully prevented the progression of hepatic disease, even though newly developed drugs have been used to treat chronic liver disorders, these drugs have often side effects (Bruck *et al*., 1996). Therefore much attention has been focused on natural antioxidants. These antioxidants occur in all higher plants and in all parts of the plant (wood, bark, stems, pods, leaves, fruits, roots, flowers and seeds).

The use of medicinal plants for health started from thousands of years and still a part of the medical practice in Egypt and other developed countries.

Dill *"Anethum graveolens* L." has been recognized in different system of traditional medicines for the treatment of different diseases and ailments of human beings. Preliminary phytochemical screening of this plant revealed the presence of flavonoids, essential oil, phenolic compounds. It has been reported as antibacterial, antispasmodic, antiulcer activity, antioxidant, hypolipidemic, genotoxicity and diuretic effect (Heamalatha *et al*., 2011).

Dill is an annual herb which is native to Mediterranean countries and southeastern Europe, used primarily as a

Corresponding Author: Naeem M. Rabeh, Department of Nutrition and Food Science, Faculty of Home Economics, Helwan University, Cairo, Egypt

condiment. Dill seed and leaves are used as flavouring in sauces, vinegars, pastries and soups. Dill has medicinal value as a stimulant and a carminative. The dill seeds have essential oil as an active substance, while carvone and limonene are the main constituents of essential oil (Kruger and Hammer, 1996; Bailer *et al*., 2001; Singh *et al*., 2005; Callan *et al*., 2007).

The essential oil extracted from both leaves and seeds of dill, could be used in chewing gums, candies and pickles (Zohary and Hopf, 2000) and moreover provide good antioxidant activities (Singh *et al*., 2005). Carvone (38.8%), apiol (30.8%), limonene(15.9%) and trans-(+)-dihydrocarvone (10.99%) were the main components of the essential oil of *Anethum graveolens* L. seeds (Babri *et al*., 2012).

Fennel *"Foeniculum vulgare"* is a medicinal plant belonging to the family Apiaceae (Umbelliferae). The leaves, stalks and seeds of the plant are edible. Essential oil of fennel is used as flavoring agents in food products such as beverages, bread, pickles, pastries and cheese. It is also used as a constituent of cosmetic and pharmaceutical products (Piccaglia and Marotti, 2001; Boskabady *et al*., 2004; Modaress and Asadipour, 2006). Herbal drugs and essential oils of fennel have hepatoprotective effects (Ozbek *et al*., 2003). They are also known for their diuretic, anti-inflammatory, analgesic and antioxidant activities (Choi and Hwang, 2004; Miguel *et al*., 2010).

Many phytochemical studies have been conducted to investigate the chemical composition of the essential oil of fennel from different origins and have shown that the major components are phenylpropanoid derivatives and monoterpenoids (Renjie *et al*., 2010). Ethnobotanical data currently available on wild useful plants in Egypt highlight the importance of fennel's culinary and medicinal uses (Singh and Kale, 2008). Moreover, fennel (essential oil) has been used for centuries in the Mediterranean area as an aromatic herb and also in folk medicine, due to its pharmacological properties. Major components of fennel seed oil samples by chromatographic analysis contain transanethole, fenchone, methylchavicol, limonene, α-pinene, camphene, β-pinene, β-myrcene, α-phellandrene, 3-carene, camphor and cisanethole (Ozcan *et al*., 2001; Simandi *et al*., 1999).

Conventional drugs used in the treatment of liver diseases are generally inadequate and have some serious adverse effects. It is, therefore, necessary to search for alternative drugs for the treatment of liver diseases. So we aimed to examine the protective effect of Dill (*Anethum graveolens* L.) and Fennel (*Foeniculum vulgare*) oil on hepatotoxic rats.

MATERIALS AND METHODS

Rats: Thirty adult male albino rats of Sprague Dawley strain each weighing 200±5 g b.wt. were used in the study. The rats were obtained from the Laboratory Animal Colony, Helwan, Egypt. The animals were housed under hygienic conditions in plastic cages which contain wood shavings. The animals were kept at a room temperature of 25 ± 2°C with relative humidity of 50-60% and on 12 h light/12 h dark cycle. The rats were provided free access of basal diet and water. The rats were allowed to acclimatize to the laboratory environment for 7 days before start of the experiment.

Chemicals: Dill (*Anethum graveolens L.*) and Fennel (*foeniculum vulgare*) oil were obtained from Haraz Market for Herbs and Medicinal Plants, Cairo, Egypt. Kits for biochemical analysis were purchased from The Gamma Trade Company for Pharmaceutical and Chemicals, Dokki, Egypt.

Preparation of basal diet: Basal diet was prepared according to Reeves *et al*. (1993). It is consisted of 14% protein (casein), 10% carbohydrate (sucrose), 4.7% fat (corn oil), 0.25% choline chloride, 0.18% L-Cystine, 0.8% Butyl hydroquinone, 1% vitamin mixture, 3.5% salt mixture and 5% fibers (cellulose). The remainder was corn starch up to 100%.

Experiment and grouping of rats: After one week of adaptation, rats (n = 30) were divided into two main groups. The first main group (6 rats) was used as a negative control group (-ve) and fed on the basal diet only. The second main group (24 rat) were subcutaneously injected with CCl_4 in paraffin oil (50% V/V 2 mL/kg b.wt.) twice a week for two weeks to induce chronic damage in the liver (Jayasekhar *et al*., 1997). The injected rats were divided into four subgroups (six rats each). One of them (6 rats) was fed on the basal diet used as a positive control group (+ve). However, the other subgroups (3 subgroups) were fed on basal diets and obtained orally dill oil (1 mL/kg), fennel oil (1 mL/kg) and mixture of (0.5 dill and 0.5 mL/kg fennel) oil respectively for 4 weeks.

Blood sampling: At the end of the experimental period (30 day), diets were withheld from experimental rats for 12 h and then rats were sacrificed. Blood samples were collected from the portal vein into dry clean centrifuge tubes. For serum separation, blood samples were left at room temperature to get clot and then centrifuged for 15 min at 3000 rpm. Serum was carefully aspired using a needle and transfers into dry clean test tubes and kept frozen at -10°C until chemical analysis. Liver was removed for antioxidant analysis.

Biochemical analyses: Biochemical parameters i.e., aspartate amino transferase (AST) and alanine amino transferase (ALT) (Bergmeyer *et al*., 1978), alkaline phosphatase (ALP) (Roy, 1970), serum total cholesterol

(Richmond, 1973), triglycerides (TG) (Wahlefeld, 1974), high density lipoprotein (HDL-c) (Albers *et al*., 1983), were analyzed according to the reported methods.
Meanwhile low density lipoprotein (LDL-c) was calculated according to (Friedwald *et al*., 1972) using the following equation:

$$LDL\text{-}c = TC - (HDL\text{-}c + VLDL\text{-}c)$$

where, also very low density lipoprotein (VLDL-c) was estimated according to the equation of (Friedwald *et al*., 1972), as follow:

$$VLDL\text{-}c = TG/5$$

where, serum total protein and albumin were determined according to Kingsley (1939), while serum bilirubin by was determined according to (Magos, 1960).

Preparation of liver homogenate: One gram of each frozen liver tissue was washed in ice-cold 0.9% NaCl and homogenized in ice-cold 1.15% solution of potassium chloride in 50 mM potassium phosphate buffer solution (pH 7.4) to yield a 10% (W/V) homogenate. Homogenization was performed using Sonicator, 4710 Ultrasonic Homogenizer (Cole-Parmer Instrument Co., USA). The homogenate was centrifuged at 3000 rpm for 10 min. at 4°C. The supernatant was collected and used as liver homogenated sample.

Analytical procedures: The prepared liver homogenates were used for measurement of tissue malondialdehyde (MDA) according to (Ruiz-Larea *et al*., 1994) and determine the activity of antioxidant enzyme Superoxide Dismutase (SOD) according to the method of (Kakkar *et al*., 1984).

Statistical analysis: Results were expressed as mean±SE. All data from the experiment were examined statistically by one-way analysis of variance with computerized SPSS package program (SPSS 16.00 software for Windows) by ANOVA test to test the variations among groups and Post Hoc test (Duncan's test) was used to compare group means. A $p<0.05$ was considered statistically significant.

RESULTS

The obtained results in Table 1 showed that subcutaneous administration of CCL_4 to rats significantly ($p<0.05$) increased levels of serum AST, ALT and ALP as compared to (-ve) group, indicating liver damage. CCL_4 is reported to produce free radicals, which affect the cellular permeability of hepatocytes leading to elevated levels of serum biochemical parameters like ALT, AST and ALP. Administration with dill or fennel oil or their mixture significantly ($p<0.05$) decreased the elevated serum levels of liver enzymes in CCL_4-intoxicated rats as compared to (+ve) group. Also, there is no significant differences in the level of liver enzymes between the group fed on mixture of (dill and fennel oil) and (-ve) group.

Table 1: Effect of feeding dill and fennel oil on serum AST, ALT and ALP in hepatotoxic rats

Parameters groups	AST (µ/L)	ALT (µ/L)	ALP (µ/L)
Control (-ve)	69.66±3.06^{d}	24.16±1.7^{c}	47.66±3.45^{c}
Control (+ve)	88.89±2.49^{a}	39.83±2.18^{a}	76.53±2.77^{a}
Dill oil	78.83±2.68^{b,c}	33.16±2.21^{b}	59.83±2.57^{b}
Fennel oil	81.00±2.55^{b}	36.80±2.42^{ab}	65.51±3.96^{b}
(Dill+fennel) Oil	72.33±1.68^{c,d}	26.50±1.94^{c}	48.47±2.98^{c}

*Values were expressed as Means±SE, *Values at the same column with different litters are significant at $p<0.05$

Table 2: Effect of feeding dill and fennel oil on serum total protein, albumin and bilirubin in hepatotoxic rats

Parameters groups	Total protein (g/dL)	Albumin (g/dL)	Bilirubin (mg/dL)
Control (-ve)	7.23±0.24^{a}	3.37±0.23^{a}	1.20±0.01^{b}
Control (+ve)	5.71±0.20^{c}	2.50±0.18^{b}	1.71±0.10^{a}
Dill oil	6.46±0.17^{b}	2.83±0.13^{a,b}	1.53±0.07^{a}
Fennel oil	6.39±0.18^{b}	2.69±0.20^{b}	1.63±0.12^{a}
(Dill+fennel) Oil	7.20±0.26^{a}	3.09±0.22^{a,b}	1.21±0.02^{b}

*Values were expressed as Means±SE, *Values at the same column with different litters are significant at $p<0.05$

The effect of dill and fennel oil on serum levels of Total Protein and Albumin is presented in Table 2. The data revealed that CCL_4 treatment caused significant ($p<0.05$) decreased in the levels of Total Protein and Albumin and significantly ($p<0.05$) increased the serum level of Bilirubin as compared to (-ve) group.
The administration of rats with the dill and fennel oil and their mixture significantly ($p<0.05$) increased the lowered levels of total protein, while there is no significant differences in serum Albumin for the tested groups as compared to +ve group as shown in Table 2. On the other hand, the group fed on mixture of (dill and fennel oil) had no significant differences in the level of Total Protein, Albumin and Bilirubin as compared to (-ve) group. Also, the best results were found in the group fed on mixture of dill and fennel oil, while was brought to near normal. The alkaline phosphatase is the prototype of enzymes that reflects the pathological alteration in biliary flow. The CCl_4 induced elevation of this enzymatic activity in the serum is in line with high level of serum bilirubins content. The ethanol extract of Anethum graveolens Linn CCl_4 induced suppression of the increased ALP activity with the concurrent depletion of raised bilirubins suggests the possibility of the extract to have ability to stabilize biliary dysfunction in rat liver during hepatic injury by CCl_4. The results illustrated in the Table 1 and 2 exhibit the significant hepatoprotective effects of the dill and fennel oil and their mixtures.
It is clear from Table 3 that, CCL_4 treatment caused significant ($p<0.05$) increased in the content of MDA and significantly ($p<0.05$) decreased the activity of SOD in the homogenates liver of the rats as compared to (-ve) group.

Table 3: Effect of feeding dill and fennel oil on serum malondialdehyde and superoxide dismutase in hepatotoxic rats

Parameters groups	MDA (n mol/mL)	SOD (U/mL)
Control (-ve)	42.33±2.82^{d}	85.00±2.03^{a}
Control (+ve)	75.50±2.40^{a}	56.83±2.19^{d}
Dill oil	50.66±1.74^{c}	76.00±1.94^{b}
Fennel oil	61.83±3.07^{b}	68.00±2.28^{c}
(Dill+fennel) Oil	45.00±2.44^{cd}	80.50±1.52^{ab}

*Values were expressed as Means±SE, Values at the same column with different litters are significant at p<0.05

Table 4: Effect of feeding dill and fennel oil on serum triglycerides and total cholesterol in hepatotoxic rats

Parameters groups	TG (mg/dL)	TC (mg/dL)
Control (-ve)	76.33±2.91^{b}	106.33±2.07^{d}
Control (+ve)	95.50±2.18^{a}	133.50±1.60^{a}
Dill oil	84.16±3.00^{b}	121.50±1.28^{b}
Fennel oil	78.66±2.52^{b}	118.16±1.55^{b}
(Dill+fennel) oil	80.34±2.37^{b}	112.16±2.52^{c}

*Values were expressed as Means±SE, Values at the same column with different litters are significant at p<0.05

Table 5: Effect of feeding dill and fennel oil on serum lipoproteins in hepatotoxic rats

Parameters groups	HDL-c (mg/dL)	LDL-c (mg/dL)	VLDL-c (mg/dL)
Control (-ve)	72.83±2.08^{ab}	18.23±1.12^{d}	15.26±0.58^{b}
Control (+ve)	54.50±1.76^{c}	59.90±3.19^{a}	19.10±0.43^{a}
Dill oil	65.83±2.13^{b}	38.83±1.97^{b}	16.83±0.60^{b}
Fennel oil	72.33±2.83^{ab}	30.10±2.51^{c}	15.73±0.50^{b}
(Dill+fennel) oil	79.33±2.55^{a}	16.76±1.99^{d}	16.06±0.47^{b}

*Values were expressed as Means±SE, Values at the same column with different litters are significant at p<0.05

Treatment with both dill and fennel oil or their mixture significantly (p<0.05) prevented the elevated content of MDA and significantly (p<0.05) increased activities of SOD enzymes in homogenates liver of CCL_4-intoxicated rats. Also, the best results were found in the group fed on mixture of dill and fennel oil, while was brought to near normal.

The results recorded in Table 4 and 5 illustrated that subcutaneous administration of CCL_4 to rats significantly (p<0.05) increased levels of TG, TC, LDL-c and VLDL-c and significantly (p<0.05) decreased serum levels of HDL-c as compared to -ve group. The treatments with the dill and fennel oil or their mixture significantly (p<0.05) decreased the elevated serum levels of TG,TC LDL-c and VLDL-c and significantly increased the level of HDL-c as compared to +ve group.

DISCUSSION

Recently, a few hepatoprotective drugs and that too from natural sources, are available for the treatment of liver disorders. Hence, people are looking at the traditional systems of medicine for remedies to hepatic disorders. Plants have been a rich source of effective and safe medicines. Due to their safe, effective and inexpensive nature, so we aimed to investigate the hepatoprotective effect of Dill (*Anethum graveolens L.*) and Fennel (*foeniculum vulgare*) oil on liver damage induced by CCl_4 in rats.

Liver is one of the vital organs in the body and it is responsible for detoxification of toxic chemicals and drugs. Thus it is the target organ for all toxic chemicals. Carbon tetrachloride is one of the most commonly used hepatotoxins in the experimental study of liver disease (Parola *et al*., 1992). It is widely used to induce liver damage because it is metabolized in hepatocytes by cytochrome P450, generating a highly reactive carbon centered trichloromethy radical (Johnson and Kroening, 1998). These activated radicals bind covalently to the macromolecules and induce peroxidative degradation of membrane lipids of endoplasmic reticulum rich in polyunsaturated fatty acids. This leads to the formation of lipid peroxides. This lipid peroxidative degradation of biomembranes is one of the principle causes of hepatotoxicity of CCl_4 (Poli, 1993). This is evidenced by an elevation in the serum marker enzymes namely AST, ALT, ALP, total bilirubin and decrease in total protein and albumin.

Naturally occurring antioxidants can be used to protect human beings from oxidative stress damage (Scalbert *et al*., 2005). Fennel was known as excellent sources of nature antioxidants and contributed to the daily antioxidant diet (Shahat *et al*., 2011). The volatile oil of fennel showed strong antioxidant activity in comparison with butyrated hydroxyanisole and butylated hydroxytoluene (Singh *et al*., 2006).

Volatile components of fennel seed extracts contain β-myrcene (Ozbek *et al*., 2004) that elevates the levels of apoproteins CYP2B1 and CYP2B2, which are subtypes of the P450 enzyme system (De-oliveira, 1997). The cytochrome P450 (CYP) enzyme system consists of a superfamily of hemoproteins that catalyse the oxidative metabolism of a wide variety of exogenous chemicals including drugs, carcinogens, toxins and endogenous compounds such as steroids, fatty acids and prostaglandins (Shimada *et al*., 1994).

The mechanism of the hepatoprotective action of the fennel oil is uncertain but may be related to the ability of the fennel oil to inhibit lipid peroxidation in the liver and decreasing levels of serum AST, ALT, ALP and bilirubin. The CCl_4 induced hepatotoxicity produced in rats leading to hepatic injury triggers the generation of toxic radicals which can be masked by using a correct antioxidant in adequate amount. The presence of D-limonene and β-myrcene of the fennel oil explain its role in hepatoprotection by inhibiting the free radicals mediated damage (Ozbek *et al*., 2003).

The hepatotoxicity produced by chronic carbon tetrachloride administration was found to be inhibited by Foeniculum vulgare essential oil with evidence of decreased levels of serum AST, ALT, ALP and Billirubin (Hanefi *et al*., 2004).

The use of dill and fennel oil and their mixtures in our study protects the liver from damage by CCl_4 as evident by improved biochemical markers of liver damage. This

is in agreement with the commonly accepted view that serum levels of transaminases return to normal with the healing of hepatic parenchyma and the regeneration of hepatocytes (Thabrew and Joice, 1987).

The explanation to our results were in agreement with Taher *et al.* (2007) who mentioned that active ingredients of volatile oil of dill (1000 µL/kg) are D-carvon and D-limonen and may act as an antioxidant or to decrease the production of free radicals, causing stabilization of hepatocyte membrane and decreasing the release of enzymes into the blood.

Also our results were agreement with Choi and Hwang, (2004) who reported that fennel essential oil significantly increased the specific activities of SOD and Catalase. Also, the essential oil of fennel exhibited antibacterial and antiviral activities (Ruberto *et al.*, 2000).

The increase in MDA level in liver induced by CCl_4 suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanism to prevent formation of excessive free radicals. Treatment with either dill or fennel oil and their mixture significantly reverses these changes. Hence it is likely that the mechanism of hepatoprotection of either dill or fennel oil and their mixture is due to its antioxidant effect.

Oral administration of the essential oil of *Anethum graveolens* seeds, at two different doses, reduced the triacylglyceride levels by almost 42%. The total cholesterol level was not reduced by the same doses of the essential oil (Yazdanparast and Alavi, 2001).

Hajhashemi and Abbasi (2008) indicated that, *Anethum graveolens* essential oil (AGEO) was prepared by hydrodistillation and analyzed using GC/MS. AGEO had a yield of 2% and GC/MS analysis showed that alpha-phellandrene (32%), limonene (28%) and carvone (28%) were its major components. Daily oral administration of AGEO to rats at doses of 45, 90 and 180 mg/kg for 2 weeks significantly and in a dose-dependent manner reduced TC, TG and LDL-C. AGEO also increased significantly HDL-C. sothat *Anethum graveolens* has significant lipid lowering effects and is a promising cardio protective agent. These results were in agreement with our study.

Conclusion: The efficacy of any hepatoprotective material is dependent on its capacity of either reducing the harmful effect or restoring the normal hepatic physiology that has been distributed by a hepatotoxin, the results of the present study indicated that under the present experimental conditions, both dill and fennel oil and their mixtures showed hepatoprotective effects against carbon tetrachloride induced liver damage in albino rats.

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