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Research Article

Physiological and Histological Effects of Fennel Seeds (*Foeniculum Vulgare*) on Kidneys in Male Rats

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ABSTRACT

The present study aims to investigate the side effects of fennel seeds *Foeniculum vulgare* in male rats on the weights, histological changes and some of the physiological parameters of the kidney. The end of each experiment was followed by weighing the animals. Blood sample of each animal was collected by heart puncture then directly centrifuged, and the serum was kept at -80 °C for biochemical analysis and some histological standards, the animals were dissected, then the kidney was excised and fixed in neutral buffered 10% formalin for histological preparation. The increment in Urea, Total Protein and Creatinine. The result could be related to the high dose of fennel and duration of the study, which caused degeneration and necrosis of kidney cells and damage to peri tubules that led to prevention of secretion which raised Urea levels in the blood.

Keyword: *Foeniculum vulgare*; urea; total protein; creatinine; necrosis

INTRODUCTION

F. vulgare was known as a culinary herb also useful for the pharmaceutical industry for its high content in 1,8-cineole, linalool, fenchone and estragol [1]. Healthy importance of fennel comes from its numerous chemical compounds, such as volatile compounds, flavonoids, phenolic compounds, amino acids, and fatty acids. Hence it has been used for abundant types of disorders [2]. Fennel shows antispasmodic activities [3]. And as curative in infantile colic [4].Different techniques carried out the antifungal and antioxidative potentials of fennel[5]. Also can be used to reduce the potential of lung cancer, asthma and prevent thrombosis and atherosclerosis [6]. As it improves the milk supply of a breastfeeding mother, so it has been used as a galactagogue that occurs due to the presence of phytoestrogens present in fennel which promote the growth of breast tissue [7].

The kidneys are two symmetrical, bean-shaped, reddish-brown organs [8]. The functional units of the kidney are nephrons responsible for the formation of urine[9].The primary function of kidneys is to help maintain homoeostasis by regulating the composition, volume, and the pH of the extracellular fluid environment in the body, they accomplish this through the formation of urine, which is a modified filtrate of plasma[10].

MATERIAL AND METHOD

Plant

Fennel seeds were purchased from the local markets in the Ishrin Street of Al-Baya'a/ Baghdad. They were obtained as a fennel herb for culinary use; then they were prepared to be used for the experiment.

Fennel pellet preparation

Fennel seeds about(21kg) were powdered in a seed grinder, (15.9 kg) of pellet which contained (20% soya, 10%protein of fish powder, 20% American protein, 40%corn, 10%wheat flour, and additives such as di calcium, prigmy, and antioxidants) was powdered as well by the grinder, then the components were mixed and kneaded by addition of tap water and distributed into three groups as followed:

1. group of 50 grams fennel powder + 950 gram pellet powder.

2. group of 100 grams fennel powder +900 gram pellet powder

3. group of 200 grams fennel powder+800 gram pellet powder.

Small cylinder blocks were made from this dough similar to the normal rodent pellet.

Animals:

Permission for the animal study was obtained from the National Centre for Drug Control and Research (NCDCR), Ministry of Health. In this experimental study, after an adaptation period of one week, sixty male rats were randomly divided into twelve groups of five rats each, described as following:

Group 1, 2, and 3: (control) did not receive any dose they fed with rat chow pellet only for 10, 20, and 30 days subsequently.

Group 4, 5, and 6: (the experimental groups) that respectively received 18- 20 g fennel pellet in three doses of (50, 100, and 200) g/kg every 24 hours for ten days.

Group 7, 8, and 9: (the experimental groups) that respectively received 18- 20 g fennel pellet in three doses of (50, 100, and 200) g/kg every 24 hours for 20 days.

Group 10, 11, and 12: (the experimental groups) that respectively received 18- 20 g fennel pellet in three doses of (50, 100, and 200)g/kg every 24 hours for 30 days.

Collection of Blood

The end of each experiment was followed by weighing the animals, they were fully anaesthetized by diethyl ether for several minutes, and blood samples were obtained by heart puncture. 4 ml of the blood was used to obtain sera (0.5-1.0) ml separated by centrifugation.

Collection of Organs

The animals were dissected, and their left and right kidneys were excised, washed with normal physiological saline 0.9% (NaCl), blotted with filter paper, weighed and kept in the fixative solution (neutral buffered 10% formalin) for histological study

Functions of the kidney

Measurement of Blood Urea

Serum concentration of urea in the current study was determined by enzymatic method (Urease–Modified Berthelot Enzymatic–Colorimetric)[11], according to Randox Company kit.

Measurement of Serum Creatinine

This assay was done by using colorimetric method for the determination of creatinine levels in serum [12], according to Randox Company kit.

Measurement of Total Protein

This assay was done by using colorimetric method for the determination of protein levels in serum [13], according to Spinreact Company kit.

Histopathological Preparation

The Preparation for histological sections was performed according to the method of [14].

Statistical Analysis

The Statistical Analysis System-SAS(2012) program was used to effect of difference factors in study parameters (ANOVA). Least significant difference-LSD test was used to significant compare between means in this study

RESULTS

Kidney Weight and Functions

The statistical analysis of the present study for fennel effects on left and right kidney. Weights (gm) in Figure (1), (2) shows that consumption of fennel for 10 and 20 days showed non-significant decrease in left and right kidney's weight of the experimental treated groups with

concentrations (50, 100, 200)gm/kg fennel compared to control groups, while results revealed a significant decrease ($p<0.05$) in the left kidney's weight at 30 days experimentally treated groups of (100, 200)gm/kg fennel (0.634±0.11),(0.598±0.11) (gm), respectively, in comparison with the control group (0.958±0.07) (gm) . As well, there was significant decrease ($p<0.05$) in right kidney's weight at 30 days feeding with fennel in experimental treated groups of (100, 200)gm/kg fennel (0.676±0.11) ,(0.604±0.112) (gm) respectively in comparison with the control group (0.974±0.07) (gm) . Both kidneys' weight showed non-significant decrement between experimental groups when concentrations were fixed factors with the increment of the experimental duration in concentrations (50,100, 200)gm/kg fennel. There was one exception at 30 days fennel consumption in concentration (200)gm/kg (0.598±0.11) (gm) which showed significant decrement ($p<0.05$) in left kidney weights in comparison with treated groups. The result of right kidney's weight observed, as well, one exception at 30 days fennel consumption in concentration (200)gm/kg (0.604±0.112) (gm) which showed highly Significant decrement ($p<0.01$) in comparison with treated groups.

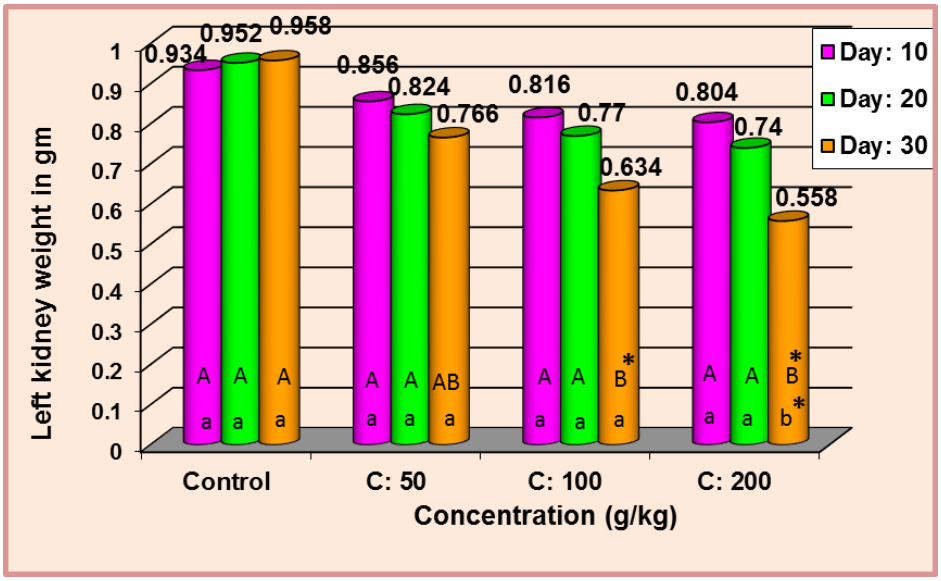

Fig. 1: Effect of different concentrations of fennel (50,100,200)gm/kg on left kidney's weight of rats with different periods of time (10,20,30) days in comparison with control groups.

**significant decrease ($P\leq0.05$).*

(A,B,C) Represent the significant difference between groups with days as a fixed factor and concentrations as a variable factor.

(a,b,c) Represent the significant difference between groups with concentrations as a fixed factor and days as a variable factor.

Statistical analysis of the present study of fennel's effects on kidney functions that included Urea, Total Protein and Creatinine in the Figures (3),(4),(5) reveals that Fennel consumption for 10 days duration showed non-significant increment in Urea level(mg/dl) in experimental groups with concentration (50)gm/kg in comparison with control group, but in 20 days duration treatment with fennel illustrated highly significant increment ($p<0.01$) in Urea level in experimental groups with concentration (100,200)gm/kg (77±8),(84±8) (mg/dl), respectively, in comparison with control group (41±8). A 30 days treatment with fennel showed highly significant increment ($p<0.01$) in Urea level in experimental groups with concentrations (100,200)gm/kg (81±8), (96±8) (mg/dl), respectively, in comparison with control group (42±7) (mg/dl). while there was non-significant increase due to fennel consumption on Urea level related with treatment duration when the concentration was a fixed factor in all treated groups when comparing between the treated groups at the same concentrations as shown in Figure (3).

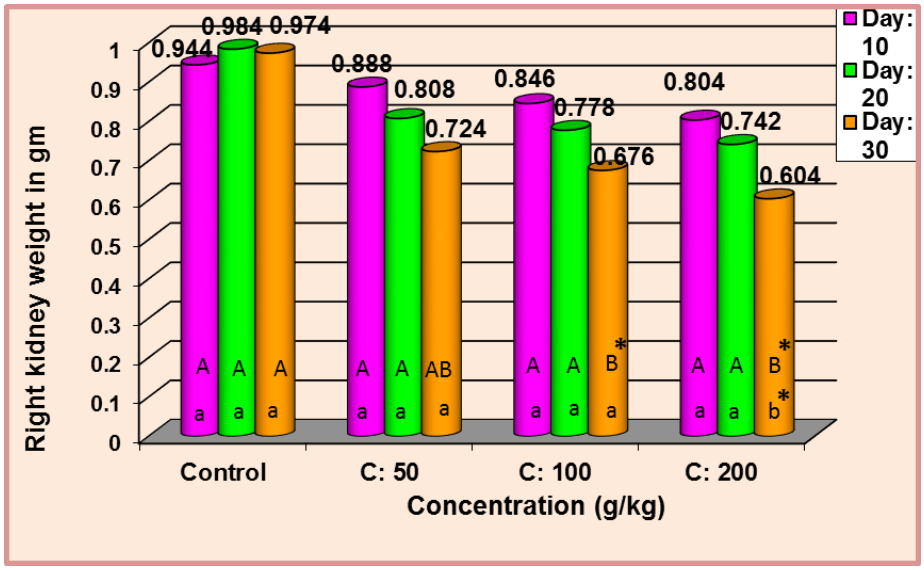

Fig. 2: Effect of different concentrations of fennel

(50,100,200)gm/kg on right kidney's weight of rats with different periods of time (10,20,30) days in comparison with control groups.

** significant decrease (P≤0.05).*

(A,B,C) Represent the significant difference between groups with days as a fixed factor and concentrations as a variable factor.

(a,b,c) represent the significant difference between groups with concentrations as a fixed factor and days as a variable factor

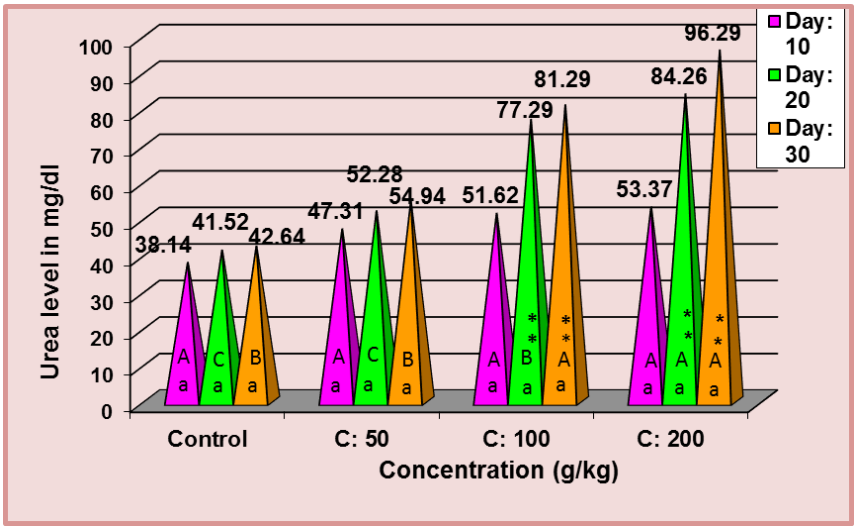

Fig. 3: Effect of different concentrations of fennel

(50,100,200)gm/kg on Urea levels of rats with different periods of time (10,20,30) days in comparison with control groups.

** Significant increase (P≤0.05).*

*** Highly significant increase (P≤0.01).*

(A,B,C) Represent the significant difference between groups with days as a fixed factor and concentrations as a variable factor.

(a,b,c) represent the significant difference between groups with concentrations as a fixed factor and days as a variable factor

Fennel consumption for 10 days duration showed non-significant increment in Total protein level(g/dl) in all experimental groups with concentration (50,100,200)gm/kg comparing with control group, while there was highly significant increment ($p<0.01$) in Total protein

level at 20 days period of time fennel feeding in experimental groups with concentration (100,200)gm/kg (12.74±1.29),(3.84±1.29) (g/dl), respectively, comparing with control group(7.39±0.60) (g/dl). As well a 30 day treatment with fennel showed highly significant increment ($p<0.01$) in Total protein level in experimental groups with concentrations (100,200)gm/kg (14.50±1.22), (16.49±1.21) (g/dl), respectively, in comparison with the control group (9.59±0.36) (g/dl), while there was non-significant increase due to fennel consumption on Total protein level related with treatment duration when concentration was a fixed factor in all treated groups when comparing between the treated groups at the same concentrations with exceptions. An exception observed in the treated group (14.50±1.22) (g/dl) with concentration of (100)gm/kg at 30 days period of time showed significant increase ($p<0.05$) in Total protein level and the other exception observed in the treated group (16.49±1.21) (g/dl) with concentration of (200)gm/kg at 30 days period showed significant increase ($p<0.05$) in Total protein level as shown in Figure (4).

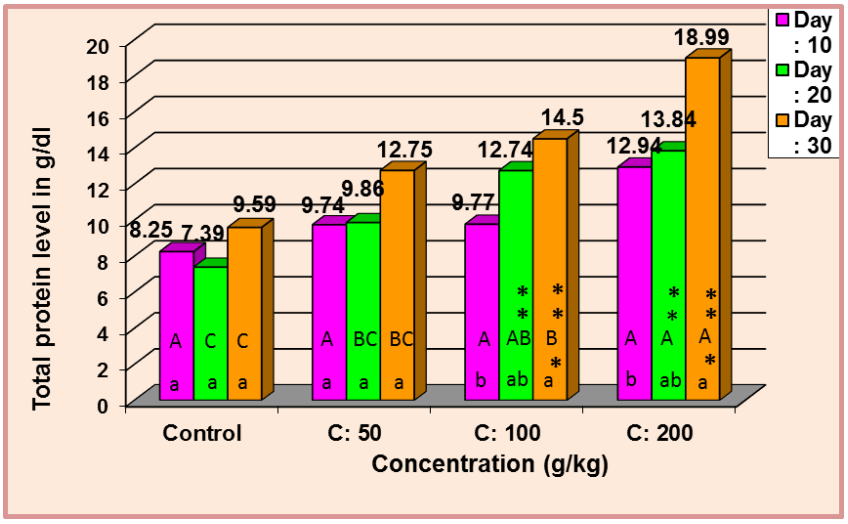

Fig. 4: Effect of different concentrations of fennel

(50,100,200)gm/kg on Total protein levels of rats with different periods of time (10,20,30) days in comparison with control groups.
** significant increase (P≤0.05).*
*** highly significant increase (P≤0.01).*
(A,B,C) Represent the significant difference between groups with days as a fixed factor and concentrations as a variable factor.
(a,b,c) represent the significant difference between groups with concentrations as a fixed factor and days as a variable factor

Fennel consumption for 10 days duration demonstrated significant increment ($p<0.05$) in Creatinine level (mg/dl) in experimental groups with concentration (100,200)gm/kg (0.689±0.05),(0.714±0.06) (mg/dl), respectively, in comparison with the control group (0.550±0.02) (mg/dl). There was as well highly significant increment ($p<0.01$) in Creatinine level at 20 days period of time fennel feeding in experimental groups with concentration (100,200)gm/kg (0.854±0.04),(0.926±0.05) (mg/dl), respectively, comparing with the control group(0.546±0.01) (mg/dl). Furthermore, a 30 days treatment with fennel showed highly significant increment ($p<0.01$) in Creatinine level in all experimental groups with concentrations (50,100,200)gm/kg (0.986±0.04), (1.216±0.09),(1.314±0.10) (mg/dl), respectively, in comparison with the control group (0.550±0.02) (mg/dl). Statistical analysis results even demonstrated highly significant increment ($p<0.01$) in Creatinine level related with treatment duration when concentration was a fixed factor in comparison with the treated groups in each concentration. as shown in Figure (5).

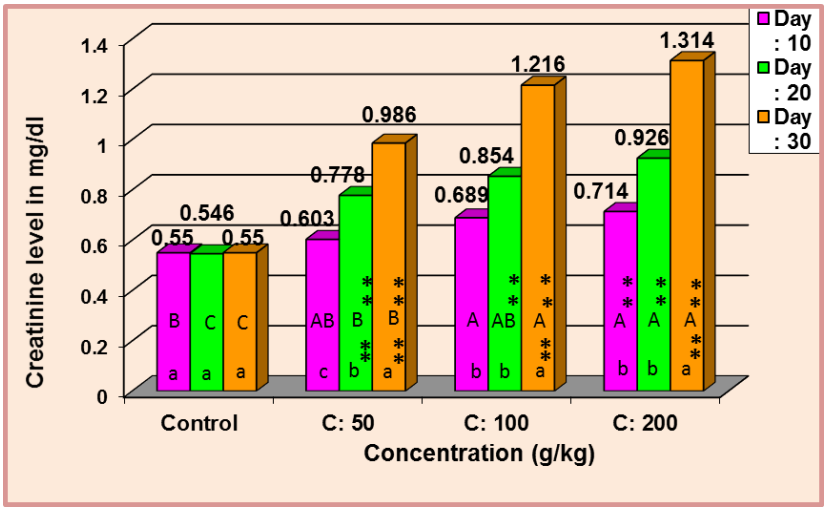

Fig. 5: Effect of different concentrations of fennel

(50,100,200)gm/kg on Creatinine level of rats with different periods of time (10,20,30) days in comparison with control groups.
** significant increase (P≤0.05).*
*** highly significant increase (P≤0.01).*
(A,B,C) Represent the significant difference between groups with days as a fixed factor and concentrations as a variable factor.
(a,b,c) Represent the significant difference between groups with concentrations as a fixed factor and days as a variable factor.

Results of the present study are in agreement with previous reports of fennel components causing decrement of kidney's weight. In a 90 days feeding study which was conducted in male and female mice that received doses for trans-anethole of (30, 60, 120 and 240)mg/kg bw per day, results showed that doses of (120 and 240) mg/kg bw per day caused significant decrease in kidney's weight [15]. Another study by [16] asserted the significant decrement of kidney weights in rats after receiving trans-anethole in the diet at doses of (600, 900 and 1200) mg/kg bw per day. As well as, a study by [17]on male and female rats observed significant decrease in kidney's weight in addition to significant decrease in total serum concentration of protein and decreased in blood urea nitrogen in female rats at high doses after feeding trans-anethole in their diet in different doses for 90 days. Furthermore, rats showed reduction in food consumption followed by decrement in body weights. In contrast, results from a study by [18] demonstrated increment in both kidneys and body weights of mice after chronic oral treatment with the ethanolic extract of fennel. In 2014, [19] revealed that the administration of dill and fennel oil mixture to rats significantly increased the lowered levels of total protein induced by carbon tetrachloride (CCl_4). Elagib *et al* [20] recorded increased values of the total proteins fraction of blood proteins in an experiment on broiler chick fed with the diet containing cumin. But, contrary to present findings, [21] found that in broilers fed with cumin seeds at (0.15 and 0.30)% in diet showed lower values of total proteins. However, [22] study showed the increase in creatinine level with the decrease in urea level after a prolonged administration of fennel oil (250 mg/kg bw) for 28 consecutive days in rats. The ingestion of 3 mg/kg of aqueous extract of *Ferula hormonis* for six weeks resulted in a non-significant increase in total proteins with the non-significant decrease in urea levels, in addition to the decrement of body weights [23]. A 3 months study on male and female rats administered (37.5, 75, 150, 300 and 600)mg/kg bw estragole in corn oil by gavage in 5 days per week revealed significant increment of kidney weights in all dosed groups of male rats and in female rats given 75 mg/kg bw or greater [24]. Similar to the findings of this experiment, [25] has also reported increment of kidney's weight after oral administration by gavage with 75 mg/kg body

weight per day *d*-limonene to rats for 13 weeks. Elevation of urea and creatinine levels in serum were taken as an index of nephrotoxicity [26].
Considering the results of the above-mentioned studies and the differences in results from the present study, these outcomes could be related to animal species diversity, the dosage of herb used, route of administration of herbs and compounds and different durations of study.

Histological Changes of Kidney

The main histological changes in all treated rats with fennel seeds on kidney tissues in different periods of time compared to control groups is shown as follows:
Kidney sections showed different histological changes after treatment with fennel in the concentration of 50gm/kg of body weight for ten days, included mild degeneration effect in the renal epithelial cell of both distal and proximal convoluted tubules Figure (7). In a period of 20 days, it showed approximately similar effects to the 30 days fennel administration, as kidney sections showed prominent degenerative changes in the renal epithelial cells of proximal and distal convoluted tubules Figure (8) in comparison with the histological sections of kidney from control groups of rats Figure (6).
Histological changes after treatment with fennel in the concentration of 100gm/kg of body weight for ten days on kidney sections showed degeneration and necrosis of renal epithelial cells with mild inflammatory cells infiltration Figure(9). The experimental group of 20 days showed more developed changes, but the 30 days treatment with fennel illustrated the more prominent appearance of necrotic of epithelial cells and inflammatory cells infiltration Figure (10) in comparison with the histological sections of kidney from control groups of rats Figure (6).
Histological sections of kidney from treated groups with 200mg/kg of bw fennel consumption for 10 days demonstrated wide area of necrosis of the renal tubules with abundant inflammatory cells infiltration Figure (11), but it seems to show more developed effects in experimental group of 20 days period, while the 30 days duration demonstrated sections of kidney with appearance of necrosis of renal tubules with severe inflammatory cells infiltration Figure (12) in comparison with the histological sections of kidney from control groups of rats Figure (6).

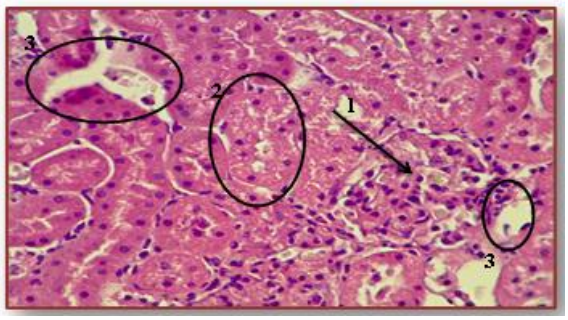

Fig. 6: Section of the normal structure of kidney from rat control Groups, Consists of: 1. Glomeruli, 2. Proximal renal tubule,3. Distal renal tubule. (400x) H&E.

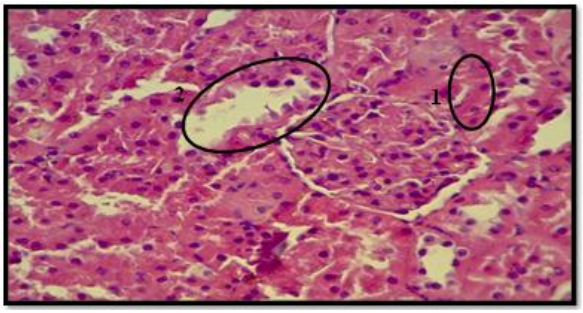

Fig. 7: Section of kidney from rat groups treated with 50g/kg of bw fennel for10 days, showing the degenerative effect in the renal epithelial cells of both 1.Proximal convoluted tubules, 2. Distal convoluted tubules(400x) H&E.

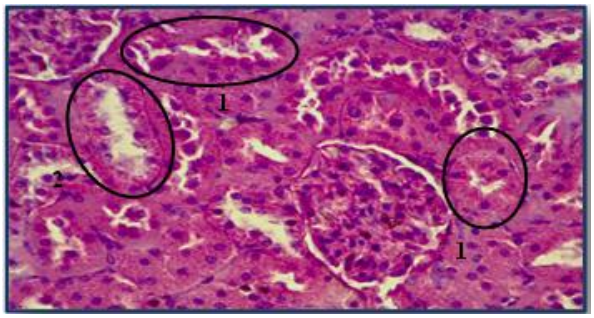

Fig. 8: Section of kidney from rat groups treated with 50g/kg of bw fennel for 30 days, showing Prominent degenerative changes in the renal epithelial cells of both: 1. Proximal convoluted tubules, 2. Distal convoluted tubules. (400x) H&E.

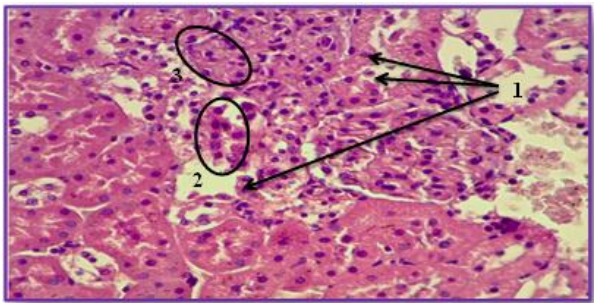

Fig. 9: Section of kidney from rat groups treated with100g/kg of bw fennel for ten days,
showing: 1.Degeneration, 2.Necrosis of renal epithelial cells, 3.Mild inflammatory cell infiltration.(400x) H&E.

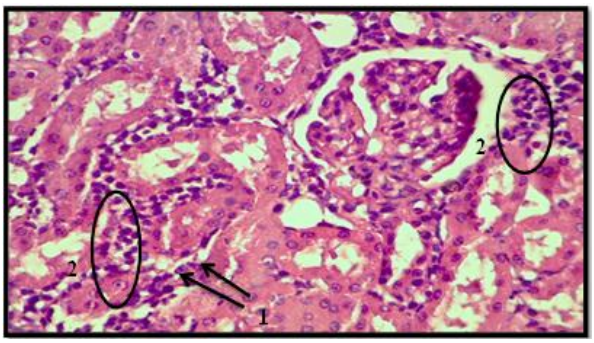

Fig. 10: Section of kidney from rat groups treated with 100g/kg of bw fennel for30 days, showing: 1.More prominent appearance of necrotic epithelial cells, 2. Inflammatory cells infiltration(400x) H&E.

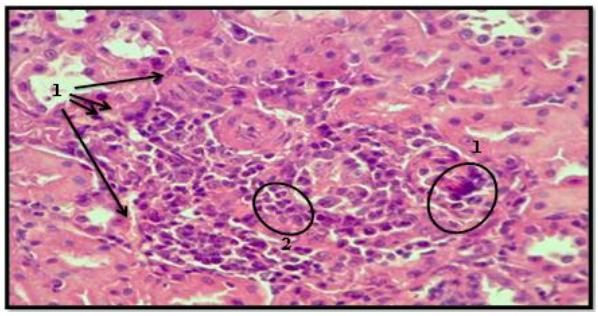

Fig.11: Section of kidney from rat groups treated with 200g/kg of bw fennel for ten days, showing: 1.Wide area of necrosis of the renal tubules, 2. Abundant inflammatory cells infiltration**.** (400x)H&E.

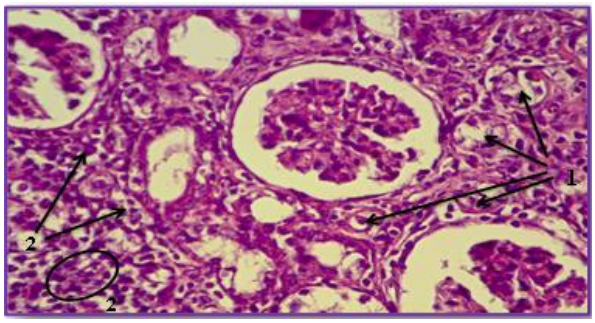

Fig.12: **Section of kidney from rat groups treated with 200g/kg of bw fennel for 30 days,** showing: 1. appearance of necrosis of renal tubules, 2.Severe inflammatory cells infiltration.
(400x) H&E.

D-Limonene is a naturally cyclic terpene and a major component of several plant essential oils (27).Oral administration to *d*-Limonene will completely be absorbed in gastrointestinal tracts of both humans and animals then rapidly distributes to various tissues, including kidney and liver (28). *D*-Limonene distributes in higher concentrations in adipose tissue, it had potent antioxidant properties and considered an excellent solvent of cholesterol (29). Some reports showed that *d*-Limonene increases the chance of hyperplasia and adenocarcinoma in rat kidney (30). Furthermore, other studies (31) demonstrate the mechanism of *d*-Limonene by causing spontaneous nephropathy, normal male rats of 30 days old exhibited marked increased protein excretion in the urine, this protein urea reached a maximum level of approximately (2.5 – 3) times that seen in females at 90 days of age, the researchers also observed microscopically intracellular droplets in the epithelial cells at the upper two-thirds of the proximal convoluted tubules of male rats kidneys of 60 days old. The results mentioned above are in similarity with a report by (30), with an addition in details that protein accumulates in the lysosomes inside the cytoplasm of epithelial cells of proximal tubules in the kidney cortex, moreover, the accumulated material becomes so abundant and crystallizes forming visible hyaline droplets, eventually the continuing of building –up droplets lead to death of epithelial cells with thining in the epithelial layers, even regeneration usually seen and the dead cell debris becomes lodged in the outer strip of outer medulla where tubules narrow forming granular casts, after that tubule dilatation occurs and necrosis in epithelial cells,

also that may cause increase in kidney weights. Unfortunately, *d* – limonene which is a major component of fennel (32) is recognised as an experimental carcinogen because it causes nephropathy and kidney tumours in male rats, that results from binding to a_{2u}-globulin in the kidney (33). Another high component of fennel is coumarin compounds that are toxic in concentrated and isolated form due to internal haemorrhage and kidney and liver toxicity (34). Also, coumarins are the carcinogen in rats causing adenomas of the kidney (35). In a study by (36) results showed that feeding broiler chicks with cumin for nine weeks lead to damage of kidney, intestine, and liver because the plant constituents may cause damage to body tissues. Oral treatment with varying doses of ethanol extract from *Petroselinum crispum* at doses >1000 mg/kg causes histopathological changes including necrosis and inflammation were observed in both kidney and liver (37).

CONCLUSION

According to the present evidence, it seems that doses and the type of herb preparations, rat species and different durations of study can be some factors affecting the results. The outcomes of the present study illustrated increment in Urea, Total Protein and Creatinine. This could be related to the high dose of fennel and duration of the study, which caused degeneration and necrosis of kidney cells and damage to peritubules that led to prevention of secretion which raised Urea levels in the blood. Also, it led to high levels of Creatinine and Total protein in serum because of the imbalance that occurred in the kidney functions. According to the present evidence, it seems that wide area of necrosis of the renal tubules with severe inflammatory cells infiltration refers to chronic damage to kidney functions caused by *d*-limonene and coumarins from fennel, chemicals at carcinogenic doses produce acute necrosis and inflammation. In adults organs, the balance between cell death and cell proliferation controls organ size, many classes of toxic chemicals are capable of inducing acute cell injury followed by death.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.

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