Studying the Toxicity of Hydroalcoholic Caraway Seeds Extract in Female Rats

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Abstract

Caraway seeds are widely used as spice for flavoring and seasoning foods, like bread and salads, because of their pungent and anise like flavor and aroma. *Carum carvi* was utilized in folk medicine for the management of many diseases. It is useful in hypothyroidism, liver and gall bladder problems, common cold, fever, bronchitis, diarrhea, and eczema. It also relives GIT spasms, fullness feelings and relieves baby's flatulent colic. The extracts of caraway have diverse compounds, including carvone and limonene, linalool, γ-terpinene and α-pinene. One or combination of these compounds may participate in the pharmacologic effects of caraway. Aim of this study was to assess toxicity of caraway extract on female rats. Carium carvi extract submitted to chemical analysis (Phytochemical screening and Gas chromatography-mass spectrometry (GC-MS) analysis). Acute toxicity study has been performed using 24 female rats divided randomly in 4 groups (n=6 for each group) that received different doses of hydroalcoholic seed extract of caraway 1000, 3000 and ,5000 mg/kg for 14 days. On day 15, the rats were euthanized and whole blood collected to examine complete blood picture. The liver, kidney and the heart have been harvested for histopathologic study and relative organ weight changes. Caraway extract considered relatively safe on blood profile and immune system within the studied doses, as it shown a non-significant change on complete blood counts (CBCs) in a dose-dependent manner (Hb and RBCs increased slightly, while WBCs and PLTs decreased slightly) and without any change in body weight and relative weight percentage of different organs. As conclusion, hydroalcoholic extract of caraway seeds was relatively safe in rats at a dose up to 5000 mg/kg

Key words: hypothyroidism, caraway seeds, toxicity.

دراسة سمية مستخلص الكحول المائي لبذور الكراويه في اناث الجرذان المختبريه

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الخلاصة:

تُستخدم بذور الكراوية على نطاق واسع كتوابل للاطعمة مثل الخبز والسلطات وذلك بسبب نكهتها ورائحتها اللاذعه. تستخدم الكراوية في الطب الشعبي لمعالجة العديد من الأمراض حيث انها تفيد في حالات قصور الغدة الدرقية ، مشاكل الكبد والمرارة ,نزلات البرد و الحمى ، التهاب الشعب الهوائية ، الإسهال و الأكزيما. تحتوي خلاصة الكراوية على مركبات متنوعة ، بما في ذلك الكارفون والليمونين والليناالول والبيتا تيربينين والباينين. قد يشارك واحد أو مجموعة من

هذه المركبات في التأثيرات الدوائية للكراوية .الهدف من هذه الدراسة هو تقييم سمية مستخلص الكراوية على إناث الجرذان المختبرية. تم استخلاص بذور الكراوية؛ وخضع المستخلص للتحليل الكيميائي (اختبارات الفرز الكيميائي النباتي وتحليل الطيف الكتلي للغاز (GC-MS). باستخدام 24 جرذ مقسمة عشوائياً إلى 4 مجموعات (6 لكل مجموعة) تم إجراء دراسة السمية الحادة ,تلقت الجرذان جرعات مختلفة من مستخلص البذور الكحولي المائي للكراوية 1000 و 3000 و 5000 ملغم / كغم لمدة 14 يومًا. في يوم 15 ، تم التخلص من الجرذان و أجري جمع عينات الدم لدراسة الصورة الكاملة للدم وبعد ذلك تم استخراج اعضاء الكبد والقلب والكلى لاجل دراسة التشريح االنسيجي والتغيرات النسبية في وزن الأعضاء. اعتمادا على النتائج التي ظهرت يعتبر مستخلص الكراوية آمنًا نسبيًا على صورة الدم والجهاز المناعي ضمن الجرعات التي خضعت للدراسة ، حيث لم تظهر تغيراً ملحوظا في تعداد الدم الكامل (CBCs) بالاعتماد على الجرعة ,حيث ان مستويات ال(Hb و RBCs) زاد قليلاً ، في حين انخفضت مستويات ال WBCs و PLTs بشكل طفيف وبدون حدوث أي تغير يذكر في وزن الجسم او معدلات الوزن النسبي للأعضاء المختلفة. في الختام ، يمكن الاستنتاج ان المستخلص الكحولي المائي لبذور الكراوية مأمون نسبيًا في الجرذان بجرعة تصل إلى 5000 ملغ / كغم.

الكلمات المفتاحية: قصور الغدة الدرقية ، بذور الكراوية ، السمية.

Introduction

Caraway (*Carium carvi*) is a biennial plant, of a height 30 to 100 cm, with a fleshy, fusiform taper root. The stem feature is erect, angular, grooved, filled with latex, glabrous and branched from the ground up. Rosette leaves and the cauline are glabrous and in part tri-pinnate. The lower pinna is typically extended across flowers and fruits; each central trunk and the side branches end with a compound flowering umbel of 8 to 16 umbel rays. Epicalyx and calyx are mostly non found. The florets are white or reddish and very tiny. The fruit is a schizocarp, meaning that fruit splits into single-seeded parts when ripe, that take an oblong and ellipsoid shape. It composed of 2 mericarps that are 3-6 mm long, of sickle shape, browny with five lighter, angular major ribs (caraway seeds) [1]. Caraway is regional to Europe and West Asia. Recently, caraway implanted in various regions of the world (from Northern Europe to the Mediterranean regions, Russia, Iran, Iraq, Indonesia and North America) [2-3]. Duke *et al.* (2002), have referred that caraway side effects or hazards are not found while using the appropriate therapeutic dosages. Overdoses for long times can result in liver and/or kidney damage [4]. In the ESCOP monograph (European Scientific Cooperative on Phytotherapy) obtained from two various studies, the acute oral median lethal dose (LD50) of caraway oil in rats was 3.5 ml/kg and 6.7 g/kg (equivalent to 7.4 ml/kg), respectively, while in rabbits was reported as 1.8 ml/kg [5]. Similarly, the LD50 of intraperitoneal dose of d-carvone in mice was 484.2 mg/kg [6]. Regarding d-limonene, the oral LD50 in a mouse of both sexes was cited to be 5.6 and 6.6 g/kg, respectively, whilst LD50 in both rat's gender was cited to be 4.4 and 5.1 g/kg, respectively [7]. Aim of the study was to evaluate the effect of caraway seeds hydroalcoholic extract on observational findings, hematologic profile, body weight changes, and other organs functions in female rats.

Materials and Methods:

Plant: *Carium carvi* seeds were supplied from Baghdad/Alshorga local market in January 2019; these seeds had been examined by a professional plant taxonomist in the pharmacognosy department/ College of Pharmacy/ Mustansiriyah University.

Extract preparation: *Carium carvi* seeds (3500 g) were dried naturally and pulverized by electrical mill (Clatronic, Germany), immersed in rich volume of ethanol: water (70:30) for one hour and extraction take place by using soxhlet's system (Quick-fit, USA) which was retain for 48 h to ensure that a complete extraction process is finish. The extract then undergoes shaking, filtering and evaporation in a rotary evaporator (Heidolph, Germany) under low pressure

till a semisolid paste weighing (500g) was achieved.

Animals: twenty-four female Wistar rats have weights between (180-230) grams obtained from the animal house of the College of Pharmacy / Karbala University and was accepted by the ethics committee for animal experimentation of College of Pharmacy/Mustansiriya University. Before beginning the intended study, animals were stand under controlled conditions of temperature 22±2° C and light of 12-12 hrs light/dark cycle by artificial lighting system, preserved in plastic cages of (20x25x35 cm), fed by free excess to rat pellets and water *ad libitum*.

Acute toxicity study: randomly divided twenty- four female rats into four groups (n=6 for each). First control group received 10% DMSO (Dimethyl sulfoxide) (10 ml /kg) by gavage. *Carium carvi* seeds extract administered as single dose after dissolving in DMSO was supplied with oral gavage to second, third and fourth group at doses of 1000, 3000, and 5000 mg/kg, respectively (table 1). Over the period of 14 days and on daily basis, the animals examined for death (if any) or any possible toxic marks like the change in behavior, movement, and body weight changes which were based on the following equation [8].

$$\% \text{ of body weight change} = \frac{\text{final weight} - \text{initial weight}}{\text{final weight}} \text{ X } 100$$

On day 15, rats were euthanized by xylazine and ketamine overdose, liver, kidney and the heart have been obtained for histopathologic assay and relative organ weight changes according to following equation [8]:

$$\% \text{ of relative organ weight change} = \frac{\text{final weight} - \text{initial weight}}{\text{final weight}} \text{ X } 100$$

Table (1): Acute toxicity groups.

Groups	n	Treatment (oral)
I: Control group	6	DMSO 10% (10 ml/kg)
II: Low dose of caraway seed extract	6	1000mg/kg in DMSO 10%
III: moderate dose of caraway seed extract	6	3000mg/kg in DMSO 10%
IV: High dose of caraway seed extract	6	5000mg/kg in DMSO 10%

n: number of rats per group, DMSO: Dimethyl sulfoxide.

Samples Collection

Blood collection: blood that collected by cardiac puncture drawing into test tube containing an anticoagulant (EDTA) (Ethylenediaminetetraacetic acid), the sample then transported to lab and the counting performed by automated hematoanalyzer that give information about percentage of blood components in a given sample.

Organ harvest: under anesthesia, abdominal-thoracic cavity of animals was opened. Liver, kidney and heart all separated for studying toxic effect of caraway seeds. After that, washing organs with distilled water then transferred to 10 % buffered formalin for further microscopical evaluation.

Measurement of complete blood counts by automated hematoanalyzer

Automated cell counters by utilizing electrical and optical mechanisms jointly by using automated analyzer (Fujifilm Corporation, Japan) being possible to examine the blood, as well as quantifying, classifying, and describing cell populations. [9].

Tissue preparation for histopathological examination: liver, kidney and heart were manipulated for histopathological studying

utilizing paraffin sections technique based on the method illustrated by Junqueira *et al*. [10]. Tissues were cut off into 3 mm slices, immerse in formaldehyde solution of 10% concentration, and after that dried utilizing succeeding raised strengths of ethanol 1 minute in each. Tissue cleaning was performed by using xylene to remove alcohol and to provide the tissues with some degree of transparency, after that the tissue impregnate with paraffin wax, heated and blocked by discharging in established templates, the mold was shifted to leica cold plat to solidify, then the blocks were kept in the refrigerator at 4 °C. Microtome used to cut off the blocks into 4µm thickness preparing it for haematoxyllin and eosin staining (H&E), washed in water bath and transferred into the oven for dewaxing, finally stained with haematoxyllin and eosin stain (H&E) to be ready for examination under light microscope with professional pathologist

Statistical analysis: the data were presented by mean± standard error mean (M±SEM). Analysis of data was done by using statistical package of SPSS-16.0 (Statistical Packages for Social Sciences-version 16). The significance of different means was established by using Analysis of variance (ANOVA) followed by the post-hoc Tukey test. Statistical significance difference was considered when *P*-value less than 0.05.

Results

Complete Blood Count (CBC): Complete blood count cells study revealed that caraway hydroalcoholic seeds extract is relatively safe on blood profile since it gives non-significant (*P*-value >0.05) differences among control group, that received vehicle, and the other three groups that received caraway seeds extract at different doses (table 2).

Table (2): Complete blood count study for control and treated groups with different doses of caraway seeds extract.

Groups	n	RBCs(1012/L)	Hb (g/dl)	WBCs(109/L)	PLT(109/L)
10%DMSO (10ml/kg)	6	5.9±0.63	10.9±2.12	5.4±1.13	6.19±1.09
Caraway seed extract (1000mg/kg)	6	6.3±0.18	13.3±0.31	5.0±1.10	6.17±1.02
Caraway seed extract (3000mg/kg)	6	6.8±0.16	13.9±0.50	4.7±0.75	6.06±1.00
Caraway seed extract (5000 mg/kg)	6	6.8±0.40	14.5±0.71	4.4±0.77	6.06±1.02

Data were reported as means ± SEM
n: number of rats per group, DMSO: dimethylsulfoxide, SEM: standard error of the mean. RBCs: red blood cell, Hb: hemoglobin, WBCs: white blood cell, PLT: platelet
All P-values were >0.05 and considered statistically non-significant among studied groups.

Observational findings: hydroalcoholic extract of *Carium carvi* seeds produce a notable change in physical activity and behavior, but without marked changes on body weight, relative organ weight of the liver, kidney and heart along the period of follow up among different selected doses (table 3). Also, toxic symptoms and mortality were absent up to the dose level of 5000mg/kg body weight in the treated rats.

Table (3): Percent of body weight changes and relative organs weight in different doses of *carium carvi* seeds extract.

Groups	n	%Body weight changes	%Relative kidney-weight changes	%Relative liver-weight changes	%Relative heart weight changes
10%DMSO (10ml/kg)	6	11.6±1.4	0.67±0.07	2.7±0.15	0.39±0.01
Caraway seeds extract (1000mg/kg)	6	11.5±1.3	0.66±0.08	2.6±0.27	0.37±0.02
Caraway seeds extract (3000mg/kg)	6	10.9±6.4	0.62±0.10	2.4±0.43	0.39±0.02
Caraway seeds extract (5000mg/kg)	6	10.8±2.2	0.55±0.5	2.7±0.32	0.34±0.01

Data were reported as means ± SEM
n: number of rats per group, DMSO: dimethylsulfoxide, SEM: standard error of the mean.
All P-values were >0.05 and considered statistically non-significant among studied groups.

Histopathological study: Light microscopical observation of the heart, kidney and liver show that, at all of the selected doses to study toxicity of caraway hydroalcoholic seed extract (1000,3000,5000 mg/kg), there was no changes in heart and kidney histology and the organs still apparently healthy and functioning normally (figure 1 and 2, respectively).Same thing considering liver at 1000 and 3000 mg/kg doses, but at high dose of caraway seeds extract up to 5000mg/kg, liver microscopic evaluation present with preserved lobular architecture, hexagonal structure, with very mild and non-considerable inflammatory cell infiltration (figure 3).

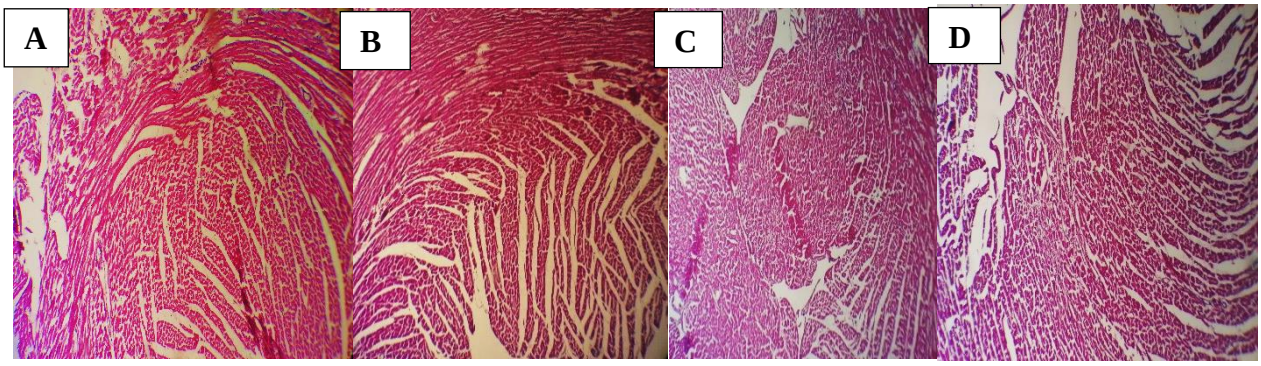

Figure (1): Histopathologic analysis of the heart demonstrating preserved myocardial fibers, intact cellular structure and cross striation.

A: Control group, B: caraway seed extract group with 1000mg/kg, C: caraway seed extract group with 3000mg/kg, D: caraway seed extract group with 5000mg/kg. All groups show normal microscopical appearance of cardiac histology. Magnification:10X. Staining: hematoxylin & eosin.

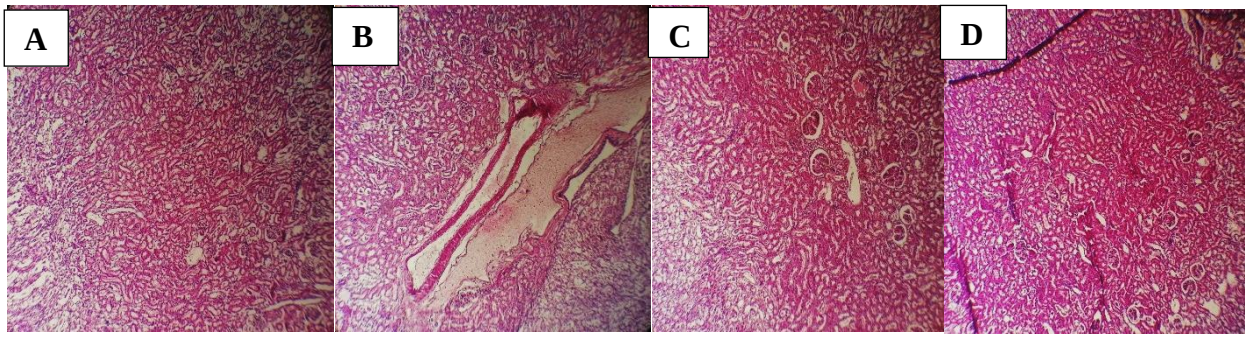

Figure (2): Histopathologic analysis of the kidney demonstrating preserved renal tissue and glomeruli tubule.

A: Control group, B: caraway seed extract group with 1000mg/kg, C: caraway seed extract group with 3000mg/kg, D: caraway seed extract group with 5000mg/kg. All groups demonstrating unremarkable microscopical changes where kidney histology is saved. Magnification: 10X. Staining: hematoxylin & eosin.

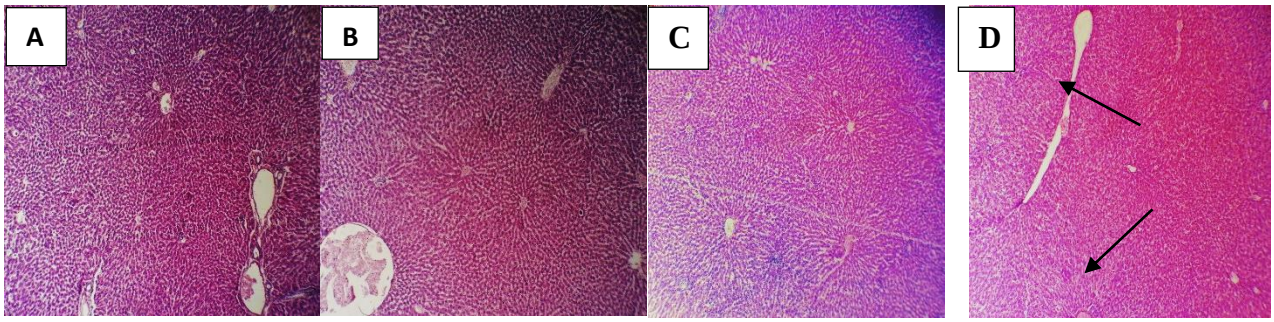

Figure (3): Histopathologic analysis of the liver demonstrating preserved hexagonal liver structure, with very mild inflammatory cell infiltration and blood vessel congestion in high dose (5000mg/kg).

A: Control group, B: caraway seed extract group with 1000/kg, C: caraway seed extract group with 3000mg/kg, D: caraway seed extract group with 5000mg/kg. All groups show unremarkable and non-considerable hepatic changes with very mild portal inflammation in group D. Magnification: 10X.Staining: hematoxylin & eosin.

Discussion: in the last decade, there was growing request for utilizing plants in therapy (back to nature) in place of utilizing synthetic medication, which may produce unwanted effects that may be more deleterious than the disease itself [11]. In the present study, caraway extract considered relatively safe on blood profile and immune system within the studied doses, as it shown a non-significant change in the levels of CBCs in a dose- dependent manner (Hb and RBCs increased slightly, while WBCs and PLTs decreased slightly). This result was in line with the study performed by Kazemipoor M *et al*. (2014), even though the later study used caraway extract for 12 weeks versus 2 weeks in the current one. The author proposed an increase in the red blood cells and reduction in platelets distribution width were obtained, this suggesting the possible advantageous effect of caraway seed extract for the management of anemia. The same author found that hyperthyroidism is accompanied with a reduction of platelet distribution width [12]. Caraway seed extracts can also conserve RBCs from destruction as a result of the existence of bioactive agents that carry out a radical-scavenging action [13].

Also, caraway seeds extract achieved a notable changes on physical activity and behavior of rats but without change in body weight and relative weight percentage of different organs. This was confirmed by Kamaleeswari *et al.* study

(2006), where the impact of different doses of caraway seed extract on the uncommon crypt foci formation in dimethyl hydrazine-induced colon cancer in rats were examined, the results showed that clinically, there is no signs of toxicity or body weight changes in the treated rats[14].

In this study, there was slight reduction in the percent of body weight in rats received different doses of caraway extracts, but it wasn't significant among them. When combined with exercise, without limitation in ingested food, caraway extract become valuable in the controlling obesity in women planning to reduce body weight, body mass index(BMI), body size, and percentage of body fat, without clinical unwanted effect. Caraway is beneficial in the controlling obesity as a result of its bioactive constituents, especially flavonoids [15].

Regarding organs toxicity, the renoprotective potential of caraway studied in animal model showing an ameliorative action of this medicinal plant versus kidney toxicity. High dose administration of caraway water extract (CWE) in rats offered nephron-protection against streptozocin-induced diabetic nephropathy, as reported by Sadiq *et al*. study (2010) [16]. As well, the same study showed a decline in the increased glucose, microalbuminuria, serum urea, total urinary volume, and creatinine after CWE administration. Additionally, the use of caraway essential oil (CEO) in infected rats result in a decrease in the renal tissue lipid peroxidation and the level of plasma urea/creatinine ratio, according to Dadkhah and Fatemi study (2011)[17]. These results referred that caraway extracts could probably give a protective effect in kidney organ instead of being toxic. The possible hepatoprotective capacity of caraway oil extract was estimated by the carbon-tetrachloride-induced hepatotoxicity test in mice. The results showed that this plant extract likely offers a hepatoprotective action by preserving the activity of xenobiotic detoxifying enzymes, including glutathione S-transferase (GST) and glutathione peroxidase (GSH-Px), raising the reduced form of glutathione (GSH) and lipid peroxidation inhibition, as shown by Naderi-Kalali *et al.* (2005) and Samojlik *et al.* (2010) studies [18-19].

In the present study, no histopathological alterations in the cardiac, renal or hepatic tissue of rats were observed at different doses of caraway extract, except a mild portal inflammation of liver, this confirm caraway-relative safety within the studied doses and term. One study conducted by Abdel-Wahab *et al.* (2017)showed that the liver histopathological samples obtained from caraway-treated rats exhibit normal structures with a moderate eosinophilic reaction in hepatocytes [20].

From the previous literature, caraway may have had a protective effect in kidney and liver function, where cadmium treated rats pretreated with caraway seeds extract show improvement the histopathological structure of kidney tubules. Liver functions improvement was examined after administration of caraway seed extract to cadmium-exposed albino rats, which preserve the liver enzymes in normal range [21]. Caraway seed extract possess ameliorative activity against cadmium-induced hepatic histological changes [20]. Data from another study also indicated that caraway essential oil provided an efficient prevention against iron oxide nanoparticles-induced hepatotoxicity in rats, depending on Abolfazl Dadkhah *et al*. study (2018) [22]. Assessment of the acute and subacute toxicity of the black caraway seed essential oil in Wistar rats was also conducted by Hadi Tabarraei *et al*. (2019). According to those researchers, utilization of black caraway seed essential oil as a treatment didn't notably induce histopathological changes in lung, liver, kidney, testes and spleen tissues [23].

For future and further work, one can measure the toxicity of caraway seeds extract other than hydroalcohol, study the

effect on other organs, and assess the subchronic, or chronic toxicity tests.

Conclusions: from data of this study, one can concludes that hydroalcoholic extract of caraway seeds is relatively safe in rats at a dose up to 5000 mg/kg.

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