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The Effect of Some Levels of Fennel Seeds Against Tramadol Toxicity Induced Oxidative Stress in Rats

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Abstract

The main objective of this study was to investigate the effect of fennel (Foeniculum Vulgare) seeds on serum parameters including kidney functions, liver enzymes, lipid profiles, malondialdehyde, superoxide dismutase (SOD), acetycholinesterase activities, total antioxidants and blood hemoglobin for Tramadol toxicity induced in rats. The experiment was carried out using thirty male albino rats weighing 145±5g. After the acclimatization period, rats were divided randomly into two main groups, the first main group (n= 6 rats) fed on the basal diet only as a negative control (normal group). The second main group (n= ٢٤ rats) were oral with tramadol hydrochloride at dose of (200 mg/kg bw.) to induce tramadol toxicity. The second main group (oral with tramadol) divided into ٤ subgroups (each 6 rats) as follow: Subgroup (1): was kept without any treatment as a positive control (+ve group) and fed on basal diet. Subgroups (2, 3 &4): were fed on basal diet containing 10%, 20% & 30 fennel seeds powder, respectively. Results indicated that, oral rats with tramadol increased. significantly all the previous parameters, except FI, BWG %, high density lipoprotein, superoxide dismutase (SOD) activity, total antioxidants and blood hemoglobin showed significant decrease compeded with all treated with levels of fennel seeds powder. The present study recommended that consuming fennel seeds improved the symptoms of tramadol toxicity and prevent its complications.

Introduction:

Tramadol hydrochloride is a racemic mixture of two enantiomers that have two complementary mechanisms of action. Tramadol use as pain

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reliever has earlier been investigated It is a synthetic opioids which has similar effects as codeine (**Schentke, 2012)**.

The mechanism of tramadol radiates around binding to μ-opiate receptors in the central nervous systems which cause inhibition of the ascending pain pathways by altering the perception. Tramadol has been used in the treatment of pains such as low back pain, osteoarthritis and migraine (**Raffa and Stone 2008**). The metabolism of tramadol occurs in the liver by the cytochrome P450 enzyme system and its byproducts are excreted through the kidneys and its completely absorbed in the upper part of the small intestine. The adverse effects of tramadol mostly noticed include: convulsion, constipation, dizziness, headache, vomiting, hyper sensitivity reaction and hallucination (**Scott and Perry, 2000 and Schentke, 2012)**.

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. **Garg et al., (2009)** reported that fennel (*Foeniculum Vulgare*) is a widely distributed plant (aromatic herb) in most tropical and subtropical countries and have long been used in folk medicine to treat obstruction of the liver, spleen and gall bladder and for digestive complaints such as colic, indigestion, nausea and flatulence. The dried aromatic fruits (seeds) are widely employed in culinary preparations for flavoring bread and pastry, in candies, as well as in cosmetic and medicinal preparations.

Fennel seeds are rich in carbohydrates, moisture, protein and fat **(Abou-Raiia et al., 2016)**. Its mineral contents are calcium, phosphorous, iron, sodium and potassium. Vitamins content are thiamine, riboflavin, niacin and vitamin C **(Bakhru, 2012)**. The major fatty acid components of fennel seeds are oleic acid and linoleic acid. Fennel seeds are rich in isoleucine and histidine **(Abou-Raiia et al., 2016)**. The seed oil yield varies according to variety and origin. The highest concentration of fennel oil ranging from 2-7%. Fennel volatile oil is a mixture of different chemicals and the main ingredients are anethole, fenchone and estragole **(Cosge et al., 2008)**.

Volatile components of fennel seed extracts by chromatographic analysis include transanethole (50 to 80%), fenchone, α –phellandrene, methylchavicol, camphor, limonene, α-pinene, camphene, ß- pinene, ß-myrcene, 3-carene, and cisanethole **(Simándi et al., 1999 and Özcan et al., 2011).**

Materials and Methods

Materials

Fennel seeds powder (Foeniculum vulgare) were purchased as dried material from local market in Cairo.

The drug tramadol (Tramadol HCl) 50 mg capsules, B.P. was a product of Zim Laboratories Ltd., India).

Animals

Thirty male albino rats, *Sprague Dawley* strain, weighing (145 ± 5g) were purchased from the animal house of Agriculture Research Center, Giza, Egypt. The animals were housed in plastic cages, maintained on a natural light-dark cycle at room temperature of 26 ± 2º C and fed standard diet according to **Reeves et al., (1993)**.

Methods

Experimental design:

The experiment was performed in Animal House in the Food Technology Research Institute, Agriculture Research Center, Giza. After the acclimatization period, rats were divided randomly into two main groups, the first main group (n= 6 rats) fed on the basal diet only as a negative control (normal group). While, the second main group (n= ٢٤ rats) were orally tramadol at dose of (200 mg/kg bw.) three times weeky, according to (**Gborienemi, 2018).**

The second main group (oral with tramadol) was divided into 5 subgroups (each 6 rats) as follows: Subgroup (1): was kept without any treatment as a positive control (C +ve group) and fed on basal diet. Subgroups (2, 3 & 4): were fed on basal diet containing 10%, 20% and 30% fennel respectively. Body weight (BW) was recorded weekly during the

experimental period and feed intake was measured daily during the experimental periods.

Blood sampling:

At the end of the experiment period (6 weeks), rats were sacrificed after overnight fasting under ether anesthesia. Blood samples were taken from hepatic portal vein, small part was taken into heparinised tube and the remainder were left to clot by standing at room temperature for 15 minutes, and then centrifuged at 3000 rpm for 20 minutes. Serum was carefully separated and transferred into clean quite fit plastic tubes and kept frozen at - 20°C until the time of analysis.

Biological evaluation:

At the end of the experiment, biological evaluation of the tested diets was carried out by determining total feed intake (FI) and body weight gain% (BWG%) according to **Chapman et al., (1959)**.

Biochemical analysis:

Determination of blood hemoglobin

Blood hemoglobin was estimated according to **Drabkin, (1949).**

Determination of serum lipids:

Enzymatic colorimetric determination of triglycerides was carried out according to **Fossati and Prencipe, (1982)**. Total cholesterol was determined by colorimetric method according to **Allian et al., (1974)**. Determination of HDL (high density lipoprotein) was carried out according to the method of **Fnedewaid, (1972).** The determination of VLDL (very low density lipoproteins) and LDL (low density lipoproteins) were carried out according to the method of **Lee and Nieman, (1996)** by calculation as follows:

***** VLDL (mg/dl) = Triglycerides /5

***** LDL (mg/dl) = Total cholesterol –HDL-VLDL

Determination of kidney functions:

Serum creatinine, uric acid and urea were determined according to the methods described by **Bohmer, (1971)**; **Fossati et al., (1980)** and **Patton and Crouch, (1977)**, respectively.

Determination of liver enzymes:

Serum alanine and aspartate aminotransferases (ALT & AST) were estimated according to **Reitman and Frankel, (1957).**

Determination of serum antioxidant parameters and acetycholinesterase

Superoxide dismutase (SOD) activity, total antioxidants capacity (TAC), and malondialdehyde (MDA) were determined according to **Nishikimi et al.,(1972); Cao et al., (1993) and Ohkawa et al.,(1979)**, respectively. Acetycholinesterase (AchE) activity was determined according to **Knedel and Boottger, (1967).**

Statistical analysis:

The obtained data were statistically analyzed using computerized SPSS (Statistic Program Sigmastat, Statistical Soft-Ware, SAS Institute, Cary, NC). Effects of different treatments were analyzed by one way ANOVA (Analysis of variance) test using Duncan's multiple range test and $p<0.05$ was used to indicate significance between different groups **(Snedecor and Cochran, 1967).**

RESULTS AND DISCUSSION

Effect of fennel on feed intake (FI), body weight gain % (BWG %) and blood hemoglobin in rats received tramadol were illustrated in table (1). It could be noticed that group received tramadol (control+ ve) recorded a significant decrease in feed FI, BWG% and hemoglobin compared with healthy control group. FI and BWG% of all treated groups increased significantly compared with untreated group, however it could not reach the normal value recorded by healthy control group. In this respect **Domingo, (1987)** found a significant decrease in body-weight gain associated with a decrease in food control +ve of body weight per day. Our findings were in agreement with those of **Tollba, (2003)** who noted that adding fennel to the

diet resulted in increased body weight**. El-Deek et al., (2003) and Soheir and Waffa, (2013)** indicated that body weight was increased and improvement feed conversion by using fennel in the diets. Fennel stimulates the flow of digestive juice in the stomach intestine and increases the efficiency of broken fats to fatty acids and affected pathogen microorganisms in digestive system and increased body weight and improved feed conversion ratio.

Concerning the mean values of hemoglobin for groups fed on diets containing fennel in at dose of 10, 20 & 30 g/kg diet showed significant increase than the positive control group. These results may be due to tramadol ions inhibit many enzymes **(Hamid et al., 2016)** and tramadol intoxicated animals showed a significant reduction in gastrointestinal iron absorption **(Cannata, 1996).** In this respect, **National Academy of Sciences, (2003)** showed that, fennel seeds in their diets had significantly higher red blood cell count, hemoglobin and packed cell volume PCV compared with the control group. The improvement in red blood cell, hemoglobin and PCV may caused by the improvement of metabolism and increase the absorption of nutrient. **EL-Shobaki et al., (2009)** found that fennel has promoted iron absorption in rats, suggesting positive use as a preventative agent in iron digestive system as it reveals flatulence and helps to improve the appetite. Fennel seeds are concentrated source of minerals like copper, iron, calcium, manganese, potassium, selenium, magnesium and zinc. Iron and copper is required for red blood cell formation **(Singh et al., 2006).**

Effect of fennel seeds on lipid profile in rats received tramadol are presented in Table (2). Total serum cholesterol and triglycerides increased significantly in the positive control group as compared to healthy group. This result in agreement with **Samira et al., (2016)** who noticed that, exposure to tramadol can affect the triglyceride metabolism and triglyceride concentrations in the body. Also, the positive control group cleared significant increase in the mean values of LDL-c and VLDL-c than the healthy rats.

All groups of rats which treated with the two levels of fennel had a significant decrease in the mean values of serum total cholesterol, triglycerides, LDL-c and VLDL-c comparing to the positive control group. The mean value of HDL-c decreased significantly in (+ve) control group compared to (-ve) control group. The percentage of decrease in HDL-c mean value for positive control group was estimated in comparison to the healthy group. The best results for all lipoproteins were noticed in the groups of rats fed on diet containing (30 g fennel /kg diet), as compared to both of all treated and the positive control groups**.**

These results were agreement with **Birdane et al., (2007)** who showed that, antioxidative properties and radical scavenging activity may be the possible mechanisms by which fennel ameliorated the total lipids, cholesterol, triglycerides and LDL-c**.** Anethole (t-anethol) that is the main compound in all fennel volatile oils possesses significant antioxidant activity. The presence of t-anethol and flavonoids content in fennel may be associated with lowering total lipids, cholesterol, triglycerides and LDL-c levels. So fennel suggested to be a new alternative for clinical management of hyperlipidemic patients **(Freire et al., 2005).**

Effects of fennel seeds on kidney and liver functions in rats received tramadol are illustrated in Table (3). Data revealed that, oral rats with tramadol led to significant increase in serum uric acid, urea and creatinine as compared to normal group of rats. Treating tramadol groups with any level from fennel seeds resulted in significant decrease in all mean values of kidney functions (serum uric acid, urea and creatinine), except the following group 30g fennel cleared non significant differences in mean values of both uric acid and urea as compared to the positive control group. Our findings in agree with **Somayyeh and Farah, (2013)** who revealed that fennel increased kidney activity and decreased urea rate. Fennel has a protective effect on the kidney during progressive glomerulosclerosis in the female rats. The finest results of kidney functions recorded for the groups of rats that fed on diet containing (10, 20 and 30g fennel seeds powder, as compared to both of all other treated and the positive control groups.

From **table (3),** it could be observed that, the mean values of serum (AST and ALT enzymes) (u/l) in the positive control group increased significantly as compared to the healthy control group. Oral rats with tramadol increased AST and ALT enzymes than that of healthy rats. In this respect, molecular changes such as DNA damages and gene suppression or expression may happen to hepatic cells when the model animal exposed to toxic materials **(Taghaddosinejad, et al., 2011).**

Addition of fennel seeds all tested levels showed a significant decrease in mean value of serum AST and ALT enzymes activity than the positive control group. **Ozbek et al., (2006)** showed that, anethole, D-limonene and β-myrcene compounds found in fennel have a potent hepatoprotective action; D-limonene increases the concentration of liver glutathione (GSH) which is required by several enzymes that participate in the formation of the correct disulfide bonds of many proteins. β-myrcene elevates the levels of apoproteins, which are subtypes of P450 enzyme system that catalyse the oxidative metabolism of a wide variety of exogenous chemicals including drugs, toxins, and endogenous compounds such as fatty acids.

Amr, (2012) reported that, feeding high fat diet supplemented with fennel seeds induced significant ($p<0.05$) decrease in serum AST, ALT and ALP levels compared to the positive control group. Ginseng extracts have been reported to show protective effects on hepatocytes in vitro and liver injury in various animal, and clinical models induced by a wide variety of hepatotoxins including hydrogen peroxide (H_2O_2) and cadmium chloride **(Shukla and Kumar, 2009 and Bak et al., 2012).**

Effect of fennel seeds on antioxidant parameters and acetyl cholinesterase in rats received tramadol were illustrated in table (4). It could be observed that the mean value of serum malondialdehyde and acetyl cholinesterase in untreated group (control+ve) was significantly higher than in healthy control group. All group-containing diets were able to reduce serum MDA and acetyl cholinesterase significantly compared with untreated group of acetyl cholinesterase. In general, the best result of MDA and

acetyl cholinesterase activity was noticed in group treated with (30g fennel/kg diet) as its mean value was the nearest from that recorded by the healthy control group. Fennel exhibited good radical scavenging activity. A significant enhancement in the activities of antioxidant enzymes were observed in diets containing fennel. **(Singh and Kale, 2008 & Nickavar and Abolhasani, 2009)**. Essential oil of fennel has also strong radical scavenging and has a strong protective effect against lipid peroxidation **(Faudale et al., 2008 and Ozcan et al., 2009).** Moreover, **Amr, (2012)** reported that feeding supplemented diets with different levels of fennel seeds increased significantly the serum activity of SOD enzyme compared to the positive control rats. Feeding rats with high fat-diet supplemented with fennel seeds significantly reduced serum MDA levels compared with positive control rats**.**

Fennel seeds reduced oxidative stress and improve antioxidant defense. This action of fennel may be related to its antioxidant activity. This effect may be due to fennel content of phenolic and flavonoid compounds which enhance the activity of antioxidant system. Flavonoid and phenolic compounds possess antioxidants which have free radical scavenging mechanism, causes potential alteration of physiological antioxidant status **(Zayachkivska et al., 2015)**. The biological activities of the flavonoids are related to their antioxidant activity by various mechanisms, e.g. by scavenging or quenching free radicals, by chelating metal ions, or by inhibiting enzymatic systems responsible for the generation of free radicals **(Mojzisova and Kuchta, 2011).**

In the body, non-enzymatic anti-oxidation including GST and enzymatic anti-oxidation including GPx, CAT, and SOD occur to protect cell membranes and intracellular materials from reactive oxygen species, including free radicals. Acetylcholine (ACh) is an important neurotransmitter that plays a critical role in memory and learning processes. In central cholinergic systems, ACh is synthesized from choline and acetyl-CoA by choline acetyltransferase (ChAT) **(Ohno et al., 2011)**. After being delivered in the synapses, ACh is hydrolyzed, resulting in choline and an

acetyl group in a reaction catalyzed by the enzyme cholinesterase (ChE) **(Ballard et al., 2009).**

Conclusion:

It could be concluded that, addition fennel seeds to the diet are effective in protect the body from the oxidative stress induced by tramadol hydrochloride.

Table (1): Effect of fennel seeds on feed intake, body weight gain % and hemoglobin in rats received tramadol

Parameters Groups	Feed intake g/day	Body weight gain %	Hemoglobin (Hb) g/dl
Normal control group	19.33±2.31 [a]	96.10±9.80 [a]	12.56±1 .95 [a]
Control group (+ve)	13.75±2.75 [c]	51.15 ±7.62 [c]	9.38±1.93 [b]
tramadol +10g fennel /kg diet	15.99±2.19 [b]	71.37 ±10.8 [b]	11.06±1.82 [ab]
tramadol +20g fennel/kg diet	16.12±2.43 [b]	71.90 ±8.48 [b]	12.30± 1.24 [a]
tramadol +30g fennel/kg diet	17.72±2.37 [b]	72.12±9.19 [b]	12.32 ±0.73 [a]

Values are expressed as mean ± SD. Significance a t p<0.05.
Values which don't share the same letter in each column are significantly different.

Table (2): Effect of fennel seeds on lipid profile in rats received tramadol

Parameters Groups	TC mg/dl	TG mg/dl	VLDL-c mg/dl	LDL-c mg/dl	HDL-c mg/dl
Normal control group	130.67± 3.79 [b]	152.00± 10.07 [c]	30.4± 4.01 [c]	57.66± 5.12 [c]	42.6± 8.46 [a]
Control group (+ve)	207.33± 19.94 [a]	241.33± 16.65 [a]	48.27± 3.33 [a]	131.07± 11.02 [a]	26.63± 8.89 [b]
tramadol +10g fennel /kg diet	138.67± 14.01 [b]	164.33± 11.01 [bc]	32.87± 5.60 [bc]	69.47± 9.71 [c]	37.33± 6.03 [a]
tramadol +20g fennel/kg diet	138.01± 14.42 [b]	199.1± 10.15 [abc]	39.82± 6.03 [abc]	59.18± 8.97 [c]	39.00± 8.19 [a]
tramadol +30g fennel/kg diet	136.33± 5.51 [b]	187.02± 11.79 [bc]	37.4± 7.28 [bc]	58.27± 7.57 [c]	40.67± 3.06 [a]

Values are expressed as mean ± SD. Significance at p<0.05.
Values which don't share the same letter in each column are significantly different.

Table (3): Effect of fennel seeds on kidney and liver functions in rats received tramadol

Parameters / Groups	Uric acid mg/dl	Urea mg/dl	Creatinine mg/dl	AST Activity (Iu/ml)	ALT Activity (Iu/ml)
Normal control group	2.73± 0.78 ^{b}	42.67± 3.06 ^{c}	1.02± 0.07 ^{b}	41.67± 8.50 ^{b}	37.67± 3.21 ^{c}
Control group (+ve)	5.20± 0.52 ^{a}	70.03± 2.65 ^{a}	1.97± 0.31 ^{a}	78.67± 9.07 ^{a}	74.67± 6.81 ^{a}
tramadol +10g fennel /kg diet	2.79± 0.72 ^{b}	56.11± 3.21 ^{bc}	1.30± 0.17 ^{b}	46.33± 6.03 ^{b}	48.33± 8.92 ^{bc}
tramadol +20g fennel/kg diet	3.82± 0.93 ^{ab}	61.67± 6.35 ^{ab}	1.41± 0.22 ^{b}	45.02± 3.46 ^{b}	46.12± 9.64 ^{bc}
tramadol +30g fennel/kg diet	2.80± 0.46 ^{b}	56.01± 8.46 ^{bc}	1.17± 0.06 ^{b}	43.01± 7.32 ^{b}	38.67± 8.08 ^{bc}

Values are expressed as mean ± SD. Significance at p<0.05.
Values which don't share the same letter in each column are significantly different.

Table (4): Effect of fennel seeds on antioxidant parameters and acetyl cholinesterase in rats received tramadol

Parameters / Groups	Superoxide dismutase (SOD) U/mL	Total antioxidants mmol/L	Malondialdehyde (MDA) mmol/L	Acetyl cholinesterase (AchE) U/L
Normal control group	198.23± 12.74 ^{a}	3.1± 0.75 ^{a}	4.47± 0.76 ^{c}	106.7± 15.28 ^{c}
Control group (+ve)	114.33± 12.01 ^{c}	1.17± 0.55 ^{b}	11.05± 1.16 ^{a}	392.6± 31.88 ^{a}
tramadol +10g fennel /kg diet	153.33± 14.81 ^{b}	1.99± 0.80 ^{ab}	5.11± 0.62 ^{c}	215.1± 29.69 ^{b}
tramadol +20g fennel/kg diet	156.01± 12.10 ^{b}	2.01± 0.09 ^{ab}	5.21± 0.32 ^{c}	235.0± 30.93 ^{b}
tramadol +30g fennel/kg diet	183.33± 14.15 ^{a}	2.73± 0.68 ^{a}	4.76± 0.43 ^{c}	139. 3± 23.93 ^{c}

Values are expressed as mean ± SD. Significance at p<0.05.
Values which don't share the same letter in each column are significantly different.

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تأثير بعض مستويات بذور الشمر ضد التسمم بعقار الترامادول المتسبب فى احداث اجهاد تأكسدى فى الفئران

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الملخص العربي

تم دراسة تأثير بذور الشمر على بعض التقديرات الغذائية (الطعام المأخوذ والنسبة المئوية للزياده فى الوزن) وتقديرات السيرم و التى تشمل وظائف الكلى، انزيمات الكبد، صورة الدهون، مالونالدهيد، سوبر اكسيد ديسميوتيز، الاستيل كولين استريز ،مضادات الاكسدة الكلية و الهيموجلوبين فى الفئران المحدث لها تسمم بعقار الترامادول . وقد اجريت هذ التجربه باستخدام ٣٠ فأر من ذكور الالبينو التى تزن ١٤٥±٥ جرام .وقد قسمت الفئران عشوائيا لمجموعتين رئيسيتين المجموعه الرئيسيه الاولى (٦ فئران) تم تغذيتها على الغذاء الاساسى كمجموعه ضابطة سالبة وتم حقنها بمحلول ملحى . اما المجموعه الرئيسية الثانية (٢٤ فأر) تم اعطائها فموي بجرعه من الترامادول (٢٠٠ ملجرم/كجم وزن الجسم) يوميا لاحداث تسمم بعقار الترامادول ثم قسمت هذه المجموعه المحقونة الى أربعة مجاميع فرعيه (٦ فئران / مجموعه) كالاتى:-

المجموعة الفرعيه (١) ظلت بدون معاملة وتم تغذيتها على الغذاء اساسى (مجموعة ضابطة موجبة)

المجموعتين الفرعيتين (2,3,4) تم تغذية الفئران على غذاء يحتوى على 10 ٪ و2٪ و30٪ من بذور الشمرالمطحون، على التوالى.

وفى نهاية فترة التجربة (٦ اسابيع) تم ذبح الفئران ثم تم تقدير عينات السيرم. وقد اظهرت النتائج ان حقن الفئران بمحلول الترامادول ادى الى ارتفاع ذو دلالة احصائية فى مستويات كل التقديرات السابقه فيما عدا الماخوذ من الطعام، الزياده المكتسبة فى وزن الجسم، الليبوبروتينات مرتفعة الكثافة، سوبر اكسيد ديسميوتيز، مضادات الاكسده الكليه والهيموجلوبين لظهور انخفاض معنوى فى كل من مستوياتهم مقارنه بالمجموعات المعالجة بمستويات مختلفة من بذور الشمر المطحون . وتوصى الدراسه بتناول بذور الشمر لتحسين الاعراض الناجمه عن التسمم بعقار الترمادول ومنع مضاعفاتها.

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