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The role of Fennel on body and organ weights and metabolites in male albino rats injected with PHZ.

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ABSTRACT:

Fennel (*Foeniculum vulgare*) is a medical plant with a high content of polyphenol, it has many antioxidant properties, also it has different therapeutic effects. The aim of the present study is to evaluate the efficacy of the fennel essential oil (FEO) on some different physiological parameters in rats injected with Phenyl-hydrazine (PHZ). Rats were divided into five groups (six rats each); control group (normal rats), FEO group (administrated daily by an oral dose of FEO, 0.5mL/kg b.w. for 14 days), PHZ group (injected intraperitoneally with a daily dose of 60 mg/kg b.w. PHZ, for 3 consecutive days), protective group (administrated daily by FEO for 11 days then injected with PHZ for 3 days) and treated group (injected with PHZ for 3 days then administered by FEO for 11 days). At the end of the experiment, blood samples were collected for determination of physiological and biochemical parameters. The results showed that the PHZ induced significant decreases in rats body weight, body organ weights, serum proteins (total protein, albumin and globulin), blood glucose level and HDL –cholesterol. Administration of FEO improved body weight, body organ weights, serum proteins, blood glucose level and lipid profile in rats injected with PHZ. In conclusion, the results of the present study revealed that the FEO has improving effects on body and organ weight.

1. INTRODUCTION

Phenylhydrazine (PHZ) is extensively used in various domains, including industry, agriculture, laboratories and medicine **(Singh *et aL., 2014)*.** It functions as a chemical intermediate in the pharmaceutical, agrochemical and chemical industries **(Shwetha *et al*.2019).** PHZ presents risks through inhalation, topical application, or oral ingestion, with reported LD_{50} values ranging from 80 to 188 mg/kg of body weight **(Berger, 2007.)** PHZ reduces rats' body weights by intraperitoneal injection at doses of 8 mg/kg **(Anbara *et al*., 2018),** 40mg/kg **(Allahmoradi *et al*., 2019),** and 60mg/kg **(Amama *et al*., 2022).** Meanwhile, PHZ increases the weight of body organs such as the liver, kidneys, and spleen **(Kale *et al*., 2019).** According to **Ezeigwe *et al*. (2019)**, PHZ affected the lipid profile in rats by causing a significant increase in TC, LDL-C, TG, and VLDL and a significant decrease in HDL-C. **(Amama *et al*., 2022)** observed that serum and urine glucose concentrations increased in rats injected with PHZ. PHZ also resulted in significant decreases in serum proteins such as total protein, albumin, and globulin **(El-Shafey *et al*., 2023).**

Fennel, widely cultivated in arid and semi-arid regions, is valued economically and increasingly used in pharmaceuticals, making it one of the most extensively utilized therapeutic herbs globally **(Tanveer *et al*.,2021).** Animal studies and limited clinical trials indicate that chronic use of fennel is not harmful. Fennel contains primary components like anethole, camphene, cymene, estragole, myrcene, fenchone, α-pinene, α-phellandrene, p-anisaldehyde, β-pinene, and γ-terpinene (**Abbas *et al*.,2021**). It also includes vitamins such as riboflavin, , thiamine, niacin and ascorbic acid **(Alghamdi *et al*., 2020).** Various phytochemicals like quercetin, coumaric acid, ferulic acid, and chlorogenic acid have been identified in this herb **(Rahimi and Ardekani,2013) (Kooti *et al*., 2014) (Rather *et al*., 2016) (Kalleli *et al*., 2019), (Mishra *et al*., 2016) (Mihats *et al*., 2017.)** Phenolics and flavonoids are the main compounds in fennel known for their antioxidant properties and therapeutic benefits for human health **(Saber. and Eshra.,2019).** Research indicates that fennel seeds contain essential minerals like iron, zinc, manganese, calcium, magnesium, sodium, potassium, and phosphorus**. (Alghamdi *et al*.,2020.)** The seeds are rich in compounds like anethole, dianethole, photoanethole, and alpha-pinene, which exhibit antioxidant, anti-inflammatory, antidiabetic, and hypolipidemic propertie **(Raslan *et al*. ,2024).**

Fennel essential oil causes an increase in body weight **(Mansour *et al.*, 2011).** Meanwhile, it decreases kidney **(Luaibi *et al.*, 2017)** and liver weight in rats **(Shahsavari *et al.*, 2022).** Fennel administration decreases plasma TG, TC, and LDL-C concentrations while increasing HDL-C levels **(Abbas *et al.*, 2021).** According to **Luaibi *et al.* (2017)**, fennel administration increases serum protein levels in rats. Blood glucose was considerably lowered after oral treatment with fennel **(Anitha *et al.*, 2014).**

2. MATERIAL AND METHODS:

2.1. Experimental animals:

Thirty male albino rats (*Rattus norvegicus*), each weighing around 150 ± 10 g, were acquired from Helwan Farm, which is part of the Egyptian Organization for Vaccine and Biological Preparations. The rats were kept under standard laboratory conditions, maintained at a temperature of 25 ± 2°C with a 12-hour light/dark cycle, and were provided with food and water for ten days prior to the start of the experiment.

2.2. Phenylhydrazine and fennel oil:

Phenylhydrazine, as a yellow powder, was sourced from Sigma Aldrich for Scientific Chemicals, located in Cairo, Egypt.

Fennel essential oil (FEO) is obtained from Elcaptain Company, which specializes in extracting oils and cosmetics in Cairo, Egypt.

2.3. Experimental design:

Animals were divided into five groups (six rats each) as follows:

The first group (control group): Normal untreated rats stayed in the experimental conditions for 14 days.

The second group (FEO group): Rats administered a daily oral dose of FEO (0.5 ml/kg b.wt.) for 14 days according to **Perveen et al. (2017).**

The third group (PHZ group): Rats injected intraperitoneally with a single dose (60 mg/kg b.wt.) of PHZ divided in 3 successive days according **to El-Shafey *et al.* (2023).**

The fourth group (FEO then PHZ group): Rats were given a daily oral dose of FEO for 11 days and then were injected intraperitoneally with PHZ.

The fifth group (PHZ then FEO group): Rats injected intraperitoneally with PHZ then after 3 days received a daily oral dose of FEO for 11 days.

At the end of the experimental periods (14 days), all animals fasted overnight. Rats of each group were weighed and anesthetized by diethyl ether inhalation **(Sinet *et al.*, 1984)**. Rats were

dissected in order to expose the posterior vena cava of each control and treated animals as previously described by **(El-Shafey and Seliem,, 2002).**

Blood samples of the six animals of each group were collected from the posterior vena cava and allowed to clot without using any anticoagulants for 1-2 h at 37˚C then centrifuged at 3000 rpm for 15 minutes. Sera were separated and stored at –20ºC for the determination of biochemical parameters.

2.4. Determination of body weight change percentages:

The average body weights of the animals were recorded at the beginning and at the end of the experimental period (14 days) to calculate the body weight change percentages (%).

$$\boldsymbol{Body\ weight\ change\ percentage}\ (\%) = \frac{(final\ body\ weight\ (g) - \ initial\ body\ weight\ (g))\ \times 100}{initial\ body\ weight\ (g)}$$

2.5. Determination of body organs weight:

The weights of the liver, spleen and kidneys of the rats were recorded at the end of the experimental period (14 days).

2.6. Determination of lipid profile:

a. Serum triglycerides concentration:

Serum triglyceride (TG) conc. was determined spectrophotometrically according to **Bucolo *et al.* (1973),** using a Spectrum kit (Egypt).

b. Serum total cholesterol concentration:

Serum total cholesterol (TC) conc. was determined using the method described by **Watson *et al.* (1960).** It was measured spectrophotometrically using a Biomed kit (Egypt).

c. Serum high-density lipoprotein cholesterol concentration:

Serum high-density lipoprotein cholesterol (HDL-C) conc. was estimated spectrophotometrically according to **Watson *et al.* (1960)** using a Biomed kit (Egypt).

d. Serum low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol concentrations:

Concentrations of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol

(VLDL-C) are calculated by the equation of **Friedewald *et al.* (1972)** as follows:

LDL-C = TC - (HDL-C) -VLDL

VLDL-C = TG/5

2.9. Determination of protein levels:

a. Total protein concentration:

Serum total protein conc. was estimated spectrophotometrically according to the method of **Koller *et al*. (1984)** using a Diamond kit (Egypt).

b. Albumin concentration:

Serum albumin conc. was determined spectrophotometrically according to **Young *et al*. (1995)** using a Diamond kit (Egypt).

c. Globulin concentration:

Globulin concentration was calculated as follows:

Globulin = total protein - albumin

d. Albumin/Globulin ratio

Albumin/globulin ratio was calculated as follows:

Albumin/globulin ratio =

Albumin/globulin

2.10. Determination of blood glucose concentration:

Blood glucose concentration was determined spectrophotometrically according to **Kaplan *et al.* (1984),** using a Spinreact kit (Egypt).

2.11. Statistical analysis:

Results are presented as means ± standard deviations of six readings. Statistical analysis of the results were completed by the one-way analysis of variance (ANOVA), followed by Duncan's multiple range test **(Duncan, 1957).** The significance level was set at ($P<0.05$) using the Statistical Package for Social Science (SPSS) computer program (version 20.00) produced by IBM Software, Inc. Chicago, USA.Figurewas drawn using Sigma plot program produced by Systat software, Inc.Chicago.USA.

3. RESULTS:

The result of present study revealed that, The PHZ treated rats group showed significant decreases ($p<0.05$) in final weight and body weight change percentage compared to the control and the FEO rat group. The FEO group showed significant increase ($p<0.05$) in final weight and body weight change percentage compared to control and PHZ treated group (table 1).

Table (1): Effect of Fennel essential oil (FEO, 0.5ml/kg b.w.) on body weights and bodyweight change percentage in phenylhydrazine (PHZ, 60 mg/kg b.w.) treated male albino rats.

Groups / Parameters	Control	FEO	PHZ	FEO then PHZ	PHZ then FEO
Final weight (g)	**186.70 ± 3.5^{b}**	**208.33±3.47^{a}**	**171.46±0.66^{c}**	**204.26±3.37^{a}**	**203.76±1.01^{a}**
Body weight change percentage (%)	**16.45 ± 2.18^{b}**	**31.05 ±4.87^{a}**	**8.02 ± 1.38^{c}**	**28.29 ± 4.41^{a}**	**27.20 ± 1.96^{a}**

Values are expressed as mean ± standard deviation (n=6 rats) ^{a,b,c,} : values in same raw with different small letters are significantly different at (P<0.05).

Data in table (2) showed the changes in relative organ weights (liver, spleen, and kidney), The PHZ treated rats group showed significant increases (p<0.05) in Liver, spleen and kidney weight compared to the control and the FEO rat group. The FEO group showed significant decrease in liver, spleen and kidney weights compared to all other treated groups.

Table (2): Effect of Fennel essential oil (FEO, 0.5ml/kg b.w.) on organs weights in phenylhydrazine (PHZ, 60 mg/kg b.w.) treated male albino Rats.

Groups / Parameters	Control	FEO	PHZ	FEO then PHZ	PHZ then FEO
Liver weight (g)	**6.03 ± 0.47^{c}**	**6.03± 0.50^{c}**	**7.9 ± 1.7^{a}**	**7.13 ± 0.37^{b}**	**7.0± 1^{b}**
Spleen weight (g)	**1.03± 0.21^{c}**	**1.3± 0.1^{b}**	**2.13± 0.12^{a}**	**1.53 ± 0.12^{b}**	**1.46 ± 0.12^{b}**
Kidney weight (g)	**0.82 ± 0.03^{c}**	**0.83 ± 0.12^{c}**	**1.53 ± 0.58^{a}**	**1.06 ± 0.15^{b}**	**1 ± 0.1^{b,c}**

Values are expressed as mean ± standard deviation (n=6 rats).
^{a,b,c,} : values in same raw with different small letters are significantly different at (P<0.05).

Serum Protein (total protein, albumin and globulin) levels of the PHZ treated group showed significant decrease (P < 0.05). compared to those of the control and the FEO groups. Serum protein levels in groups treated with (FEO then PHZ) and (PHZ then FEO) increased significantly compared to those of the PHZ group, while they were significantly low compared to their values in the control and the FEO groups (Table 3).

Table (3): Effect of Fennel essential oil, (FEO,0.5 mL/kg b.w.) on serum protein profile in phenylhydrazine, (PHZ,60 mg/kg b.w.) treated male albino rats

Groups / Parameters	Control	FEO	PHZ	FEO then PHZ	PHZ then FEO
Total protein (g/dl)	**6.84± 0.15^{a}**	**6.61 ±0.11^{b}**	**4.63±0.79^{d}**	**5.78± 0.15^{c}**	**5.33± 0.05^{d}**
Albumin (g/dl)	**3.71± 0.03^{a}**	**3.69±0.02^{a}**	**1.99± 0.02^{c}**	**3.67± 0.05^{a}**	**3.56 ± 0.02^{b}**
Globulin (g/dl)	**3.13±0.15$^{a.b}$**	**2.92±0.12^{b}**	**2.64±0.06^{a}**	**2.12±0.18^{c}**	**1.77±0.06^{d}**
Albumin/Globulin ratio (g/dl)	**1.18±0.06^{c}**	**1.27±0.06^{c}**	**0.75± 0.02^{d}**	**1.74± 0.18^{b}**	**2.01± 0.06^{a}**

Values are expressed as mean ± standard deviation (n=6 rats).
^{a,b,c,d}: values in the same raw with different small letters are significantly different at (P<0.05).

ANOVA analysis showed that there were significant decreases (P<0.05) in the concentrations of serum TG, TC, and LDL-C and an increase in the HDL-C compared to all the other groups, while rats treated with PHZ showed a significant increase (P<0.05) in the concentration of serum TG, TC, and LDL-C an decrease in the HDL-C compared to all the other groups. Groups treated with (FEO then PHZ) and (PHZ then FEO) showed significant decreases in the concentration of serum TG, TC, and LDL-C compared with PHZ group. but still significantly high compared to control and FEO groups (Table 4).

Table (4): Effect of Fennel essential oil, (FEO 0.5ml/kg b.w.) on serum lipid profile in phenylhydrazine, (PHZ, 60 mg/kg b.w.) treated male albino rats.

Groups / Parameters	Control	FEO	PHZ	FEO then PHZ	PHZ then FEO
Triglycerides (mg/dl)	57.60±1.52^{b}	56.3±0.57^{b}	82.33±1.94^{a}	54.8± 2.6^{b}	57.4±2.54^{b}
Total Cholesterol (mg/dl)	82.88±2.43^{c}	79.00± 1.0^{d}	137.00± 1.00^{a}	84.33 ±1.52^{c}	88.16± 2.31^{b}
HDL-cholesterol (mg/dl)	54.26±7.18^{a}	46.60 ± 0.53^{b}	31.46± 0.51^{c}	41.56±1.40^{b}	43.73±2.53^{b}
LDL-cholesterol (mg/dl)	15.7 ± 2.28^{d}	21.1 ± 1.60^{c}	89.06± 1.44^{a}	31.8±2.68^{b}	32.9 ± 1.43^{b}
VLDLcholesterol (mg/dl)	11.46±0.31^{b}	11.26± 0.11^{b}	16.46 ± 0.38^{a}	10.95± 0.52^{b}	11.48 ± 0.51^{b}

Values are expressed as mean ± standard deviation (n=6 rats).

^{a,b,,cd,}: values in the same raw with different small letters are significantly different at (P<0.05).

Figure (1) showed that the FEO group showed significant decreases (P<0.05) in blood glucose level compared to the control group. The PHZ group showed a significant increase (P<0.05) in the level of blood glucose compared to the control and FEO groups. Treatment with FEO after or before PHZ help to return glucose level toward control value.

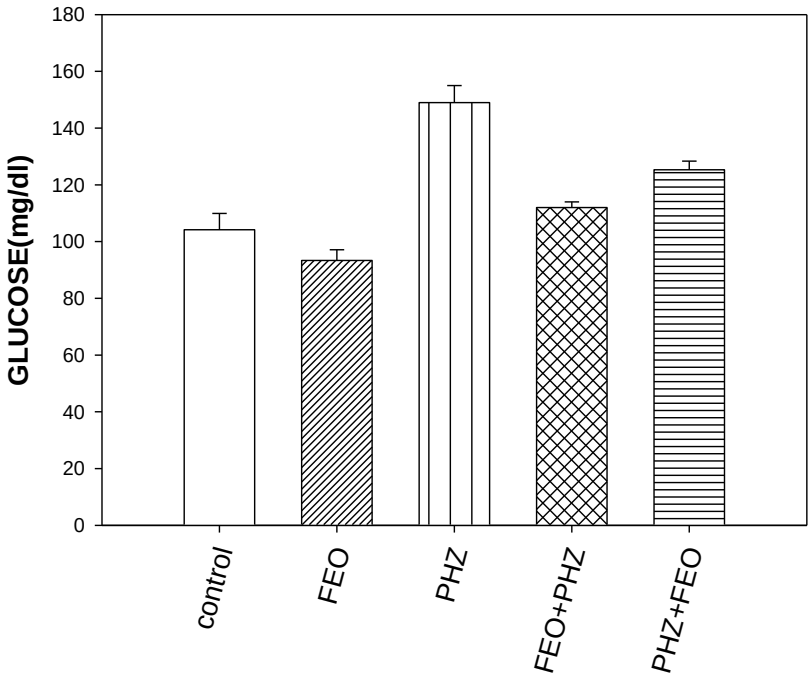

Figure (1)

3. Discussion

Phenylhydrazine (PHZ) is used as a chemical intermediate in the pharmaceutical,agrochemical,and chemical industries **(Shwetha *et al*., 2019).** PHZ is recognized as hazardous when inhaled, applied topically, or ingested, The beneficial impact of fennel essential oil (FEO) have been utilized for their hepatoprotective, nephroprotective, anti-ulcerogenic and anti-inflammatory properties.(**El-Semelawy and El-Nahhas., 2018).**

In the present study the PHZ administration showed a significant reduction in final weight and body weight change percentage, consistent with results from (**Saeedi *et al.*, 2017; Kargar *et al*., 2021)**.Mass loss in the PHZ-treated group may be due to that nutrition was decreased as a result of oxygen free radical damage to tissues resulting from the automatic oxidation of PHZ, a potent oxidantat**, (Elaby. *and Ali.*, 2018).** Also we noted that fennel essential oil increased body weight**,**These result alignment with **El-Deek *et al*. (2003) and Soheir and Waffa (2013)**. FEO 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 rat **(Badr, 2020).** Our study shows the relative percentage of organs to body mass (kidney, liver, and spleen) of PHZ group showed a significant increase in the relative percentage of kidney, liver and spleen to body mass compared to control group.

while FEO group there were no significant difference in the relative percentage of kidney, liver, and spleen to body mass compared to control this may indicates that the fennel was not toxic for their organs. This may be due to that fennel have hepato –protective effect where Fennel prevent hepatic fibrosis by influencing the control of lipid peroxidation, as the group treated with fennel had less inflammation and lipid peroxidation (**Noren , *et al.* 2023).**

Also fennel enhanced kidney function, as Fennel contain trans-anethol compound which has protective effects on, protein levels, urine production, and the kidney/body weight ratio. Additionally, it was associated with decreased tubule vascular degeneration, as well as reduced glomerular and tubulointerstitial sclerosis (**Mohamed *et al.* ,2022)**. Fennel contain trans-anethol compound which has anti-inflamatory activity for spleen and kidney and has protective effect on body organs **(*Zhang et al* .,2018)**.

Also the present study indicate a significant decrease in serum total protein, albumin, and globulin levels after The PHZ administration, these result corroborated by **Zangeneh *et al*. (2019) and Kale *et al*. (2019).** The increased proteinuria observed in the anaemic rats (PHZ)also confirms the impairment in renal function occasioned by PHZ intoxication **(Amama *et al.*,2022**). Conversely, the Fennel groups experienced a significant increase in serum protein levels compared to the PHZ groups, consistent with **Luaibi *et al. (*2017).**

In this study the albumin of the group which treated with FEO significantly decreased this may be due to antioxidant activity of fennel which has protective effect against kidney toxicity**.** Also Fennel also contains organic compounds, such as ascorbic acid, alpha-tocopherol, carotenoids, and flavonoids that work efficiently as a non-enzymatic antioxidant system to suppress reactive oxygen species (ROS) and inflammation. Exogenous antioxidants from herbal extracts reduce oxidative stress and inflammation associated with dialysis **(Barakat, *et al*.,2023)**. In our study The PHZ group experienced a marked increase in concentrations of serum TC, TG, and LDL-C alongside a decrease in HDL-C concentrations, aligning with findings from **(Ezeigwe *et al.*, 2022**). (**Zakernezhad *et al*., 2021)**.

The significant increase lipid profile may be due to that PHZ caused Hyperlipidemia and hypercholesterolemia. While FEO administration resulted in significant decreases in serum TG, TC, and LDL-C concentrations while increasing HDL-C levels, consistent with **Nadri, *et al.* (2019)**, **Abbas *et al*. (2021).** this may be due to fennel can decline the accumulation of leptin and prevent the overproduction of lipoprotein, (**Assini and Huff, 2013).** Also fennel have flavonoids which have certain contents as nobiletin, naringenin, and flavonoids were associated with significant declines in total cholesterol, LDL-C, and TG **(Zakernezhad *et al*., 2021**). **Hayes *et al*., 2002** suggested that fennel may affects the metabolic process by its estrogenic effects.

PHZ injection significantly increased blood glucose levels, in agreement with **(Amama *et al*., 2022)**. The increased in serum glucose level observed in rats injected with PHZ which may be due to that the PHZ interfered with glucose metabolism causing hyperglycaemia . while FEO administration significantly reduced blood glucose. the hypoglycemic effect of fennel essential oil may be due to increased urinary excretion of glucose, several mechanisms have been suggested for the blood-

glucose-lowering effect of fennel, including effects on energy metabolism and increase of insulin secretion from remaining pancreatic cells **(Anitha *et al*., 2014 and El-Soud *et al*., 2011).** Moreover, **Anitha *et al*. (2014)** suggested that fennel showed antidiabetic activity by reducing oxidative stress and maintaining the integrity of pancreatic beta cells. The hypoglycemic effect of fennel may be due to the presence of triterpenes, steroids, saponins and phenolic compounds.

In conclusion, PHZ has a toxic and harmful effects on body weight, organ weights and some physiological parameters. The usage of FEO after or before PHZ administration help to improve the harmful effects of PHZ.

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