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Effect of Fennel (Foeniculum Vulgare) on Appetite Hormone; Ghrelin and Adiponectin

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ABSTRACT: Adiponectin and ghrelin are two hormones that have been known as an important regulator of food intake. Traditional medicine has made use of foeniculum vulgare. We evaluated fennel effect on body weight, lipid profile, ghrelin, and adiponectin levels. 35 healthy adult male BALB/C mice that dividing into five groups including; Control, Sham, and treatment with fennel extracts in dose of 50,100 and 200 mg/kg. The injections were daily for 2 weeks. After two weeks, the serum levels of ghrelin and adiponectin were evaluated. Stomach tissue was used to measure the expression of ghrelin and adiponectin receptor by PCR. This study indicated that there was a significant reduction of cholesterol and triglycerides in 50 & 100 mg/kg (99.14285714 ± 0.525, 104.8571429 ± 0.5), and in 200 mg/kg (66.14286± 3.85714) respectively (P<0.05). Serum level concentrations of adiponectin and ghrelin were higher in the fennel 100 mg/kg (1.15625± 0.10) and 200 mg/kg (1.2595± 0.04) respectively (P<0.05). Ghrelin receptor gene expression had decreased in all treated groups; 50, 100 & 200 mg/kg (0.295469± 0.128666, 0.450276± 0.067683, 0.129677± 0.019871), respectively (P<0.05). Adiponectin receptor type 2 gene expression had decreased in all treated groups; 50, 100 & 200 mg/kg (0.5321467± 0.1134928, 0.3770703± 0.0238912, 0.4351948± 0.0667059), respectively (P<0.05). In conclusion, supplementation of fennel could improve of lipid profile, increase serum ghrelin and adiponectin concentration, and decrease their receptors gene expression, which is beneficial for health.

Keywords: Adiponectin, Fennel, *Foeniculum vulgare,* Ghrelin, Lipid Profile.

Introduction

The regulation of appetite involves intricate mechanisms where in several hormones and neuromodulators contribute to its control (Sahin *et al*., 2014; Wynne *et al*., 2005). Both genetic predisposition and environmental variables influence the regulation of energy homeostasis (Doneda *et al*., 2015). Adipose tissue has a significant function in regulating satiation and can function as an endocrine organ in addition to its primary function as an energy storage depot (Laursen *et al*., 2017; Trayhurn, 2005; Trayhurn and Wood, 2005; Mohamed-Ali *et al*., 1998). Adipokines are endocrine factors synthesized and released by fatty tissue,

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playing a crucial role in maintaining homeostasis and controlling appetite within the body (Laursen *et al*., 2017). Ghrelin and adiponectin are adipokines that are prominently involved in the regulation of energy status and hunger (Kadowaki and Yamauchi, 2005; Fatouros *et al*., 2005).

Adiponectin similarly affects the hypothalamus, although its primary function is to facilitate nutrient intake (Kadowaki *et al*., 2008). Ghrelin is synthesized and secreted through the stomach's fundus region, which is classified as an orexigenic hormone, inducing starvation (Cummings, 2006; Meier and Gressner, 2004). The alteration of these hormones' levels can improve appetite regulation. It may be employed in managing illnesses frequently linked to higher fat mass, including obesity, metabolic syndromes, and type 2 diabetes. A reduction in adiponectin and ghrelin levels could result in a diminished appetite. The alteration in hormone levels may decrease the consumption of calories, leading to a more pronounced negative energy equilibrium and consequent decrease in adipose tissue (Laursen *et al*., 2017).

Foeniculum vulgare, or fennel, is a medicinal herb utilized extensively in managing various diseases (Jang and Yang, 2018; Parejo *et al*., 2004). Numerous studies have provided that fennel essential oil has in vitro and in vivo activity concerning its anti-fungal, anti-bacterial, and anti-inflammatory properties (Soylu *et al*., 2007; Dadalioğlu and Evrendilek, 2004; Choi and Hwang, 2004). Several investigations have indicated that using fennel may have potential efficacy in enhancing conditions related to obesity and lipid diseases (Afiat *et al*., 2018; Dongare *et al*., 2012; Helal *et al*., 2011; Shahat *et al*., 2012). The study conducted by Abdelaaty *et al*. found that the administration of fennel extracts to obese rats resulted in a decrease in food consumption and body mass index (BMI), along with improvements in dyslipidemia, hyperinsulinemia, and hyperglycemia (Shahat *et al*., 2012). Additionally, the researchers demonstrated that the methanolic, aqueous, and oil extracts of fennel exhibited the potential to enhance the blood leptin levels in rats with obesity. The study conducted by Elghazaly *et al*. revealed that fennel showed a considerable capacity to reduce body weight in rats with obesity (Elghazaly *et al*., 2019).

Given the absence of any existing research on the correlation between the impacts of fennel, ghrelin, and adiponectin, both of which play significant roles in energy balance and appetite control, the objective of this study was to evaluate the influence of fennel on ghrelin and adiponectin levels, as well as body weight and serum lipid profile.

Materials and Methods

- *Animals*

35 adult male BALB/C mice were kept in a 12-hour light/dark cycle at a temperature of 22 °C and were fed standard pellets and water as needed (Arifin and Zahiruddin, 2017). All animal experiments were carried out in accordance with national standards and regulations after receiving endorsement from the Institutional Animal Ethics Committee. The Iran University of Medical Sciences (IUMS) Ethics Committee approved each experimental protocol. Additionally, all of the animal experiments that are detailed in the text were carried out in accordance with the Ethical Guidelines' guidelines for humane treatment of animals. The ethical code number "22043" from the "Iran University of Medical Sciences" supported this study.

Iran's Tehran.

- *Preparation of fennel extracts*

The Isfahan Seed Packers Company was the source of our fennel seeds. The fennel seeds were one-year-old and healthy. A grinder was used to ground the seeds to a powder for 6 minutes. Then, 2 gr of fennel powder was dissolved in 150 ml of distilled water and heated. At 90 ml volume, the solution was filtered via sterile gas. The extract was purified by pouring it into falcon tubes in equal volumes and centrifuging it at 4400 RPM for 15 minutes. Afterward, the aqueous extract was used for direct injection. The extract was prepared daily and fresh.

- *Treatment*

Thirty-five mice were assigned to one of five groups (n = 7 in each) as follows:

(i) Control (CO): intact animals left unaltered by any injections.

(ii) Sham: mice that received the solvent of fennel (Distilled water).

(iii) Fennel 50 (F50): Mice were treated with fennel (50 mg/kg; IP).

(iv) Fennel 100 (F100): Mice were treated with fennel (100 mg/kg; IP).

(v) Fennel 200 (F200): Mice were treated with fennel (200 mg/kg; IP).

Fennel extracts were injected intraperitoneal (IP) once daily for two weeks into the animals. The body weight was measured at the beginning and end of the second week of the experiment.

- *Measurement of serum ghrelin, adiponectin & Lipid concentration*

At the end of the 2nd week of the experiment, each animal was anesthetized with an IP injection of ketamine (45 mg⁄kg) and xylazine (35 mg⁄kg) mixture. Blood from the heart was collected in tubes. Subsequently, the blood samples were centrifuged, aliquoted, and transferred to the laboratory for biochemical analysis.

The concentration of ghrelin and adiponectin was assessed by employing commercially available enzyme-linked immunosorbent assay (ELISA) kits designed explicitly for Mouse (EASTBIOPHARM, USA). The values are expressed in units of nan grams per deciliter of serum. All samples were analyzed collectively in a single run. The serum triglyceride level was assessed using the GPO-PAP enzymatic technique, and the total cholesterol (TC) was determined using the CHOD-PAP enzymatic method (PARS AZMUN). The measurement of serum HDL level was conducted using the Immunoinhibition technique, and the Fried Ewald equation was utilized to determine the concentration of LDL (Friedewald *et al*., 1972).

- *BUN and creatinine detection*

Mouse-specific ELISA kits (EASTBIOPHARM, USA) were used to measure serum creatinine (SCr) and blood urea nitrogen (BUN).

- *Quantitative Reverse Rranscription PCR (qRT-PCR) Analysis*

The processes of total RNA extraction, cDNA synthesis, and qRT-PCR were performed according to previously established methods (Poorebrahim *et al*., 2018). In summary, the animals were anesthetized using the technique mentioned above. Subsequently, the stomach and liver were extracted and dissected under cold conditions. These organs were then transferred to tubes devoid of RNase, swiftly frozen by snap freezing, and subsequently kept at a temperature of -80°C until they were used for subsequent procedures. The samples were weighed, and RNA extraction was performed following the instructions provided by the AccuZolTM manufacturer's instructions (BIONEER). The extracted RNA was then dissolved in 50µl of RNase-free water. The Purified RNA samples were converted into cDNA (5µg per 20µl reaction volume) using the AccuPower ready-to-use reverse transcription kit (BIONEER). The cDNA synthesis process was carried out with a ratio of 5µg of RNA per 20µl of reaction volume. One µg of synthesized cDNA was used for SYBR Green-based real-time RT-PCR via a 2X Greenstar qPCP kit (BIONEER). The sequences of primers utilized in this investigation are listed in Table 1. The reaction conditions were 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute. Amplification specificity was checked by verifying a single peak on the melting curves. The values obtained from β-actin were utilized to load normalization in each sample. The relative gene expression changes were calculated using the ΔΔ Ct method, compared to the gene expression levels observed in control mice.

- ***Statistical analysis***

The data were presented as the mean ± standard error (SEM). The one-way analysis of variance (ANOVA) test was utilized to clarify statistically significant differences across the groups. Tukey's post hoc U test was performed when a statistically significant effect was observed. The statistical analyses were performed via SPSS version 16. The statistical significance level was established at a threshold of $p<0.05$.

Results and Discussion

- ***Analysis of body weight among the studied groups***

The results of the present investigation demonstrated no statistically significant differences in the body weight of the animals across different groups (Figure 1).

Table 1. Sequence of specific primers used for quantitative real-time revers transcription PCR

Gene Name	Primer Sequence
bactin-F	TGAAGATCAAGATCATTGCTCCTC
bactin-R	TCAGTAACAGTCCGCCTAGAAG
Ghrelin receptor-F	GTGAAGATGCTTGCTGTGGTG
Ghrelin receptor -R	GCTGAGGTAGAAGAGGACAAAGG
Adiponectin1 receptor -F	CTCATCTACCTCTCCATCGTCTG
Adiponectin1 receptor -R	GTACAACACCACTCAAGCCAAG
Adiponectin2 receptor -F	CCCGACTCTTCTCTAAATTGGATTAC
Adiponectin2 receptor -R	CAGGTAGATGAAGCAAGGTTGTG

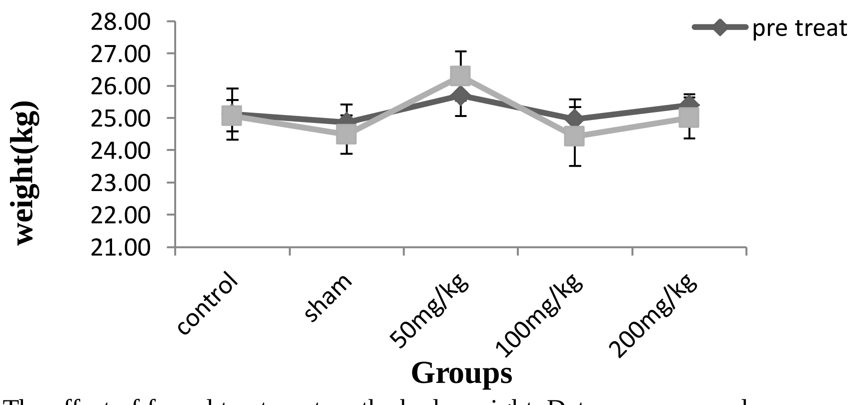

Fig. 1. The effect of fennel treatment on the body weight. Data are expressed as means ± SEM.

- *Evaluation of serum lipids in the different groups*

The analysis of serum lipid profiles in the examined groups revealed a statistically significant decrease in cholesterol concentration in the fennel 50 and 100 mg/kg groups. The concentration of TGs exhibited a notable reduction in the experimental group treated with fennel at 200 mg/kg. However, there were no statistically significant differences in the levels of LDL and HDL among the various groups (Figure. 2).

- *The impact of funnel extract on the levels of serum Adiponectin and Ghrelin*

The statistical analysis of ELISA data revealed that the plasma concentrations of adiponectin were higher in the group treated with fennel at a dosage of 100 mg/kg (Figure 3). Furthermore, the groups administered with fennel at 200 mg/kg dosage exhibited elevated plasma concentrations of ghrelin (Figure. 4).

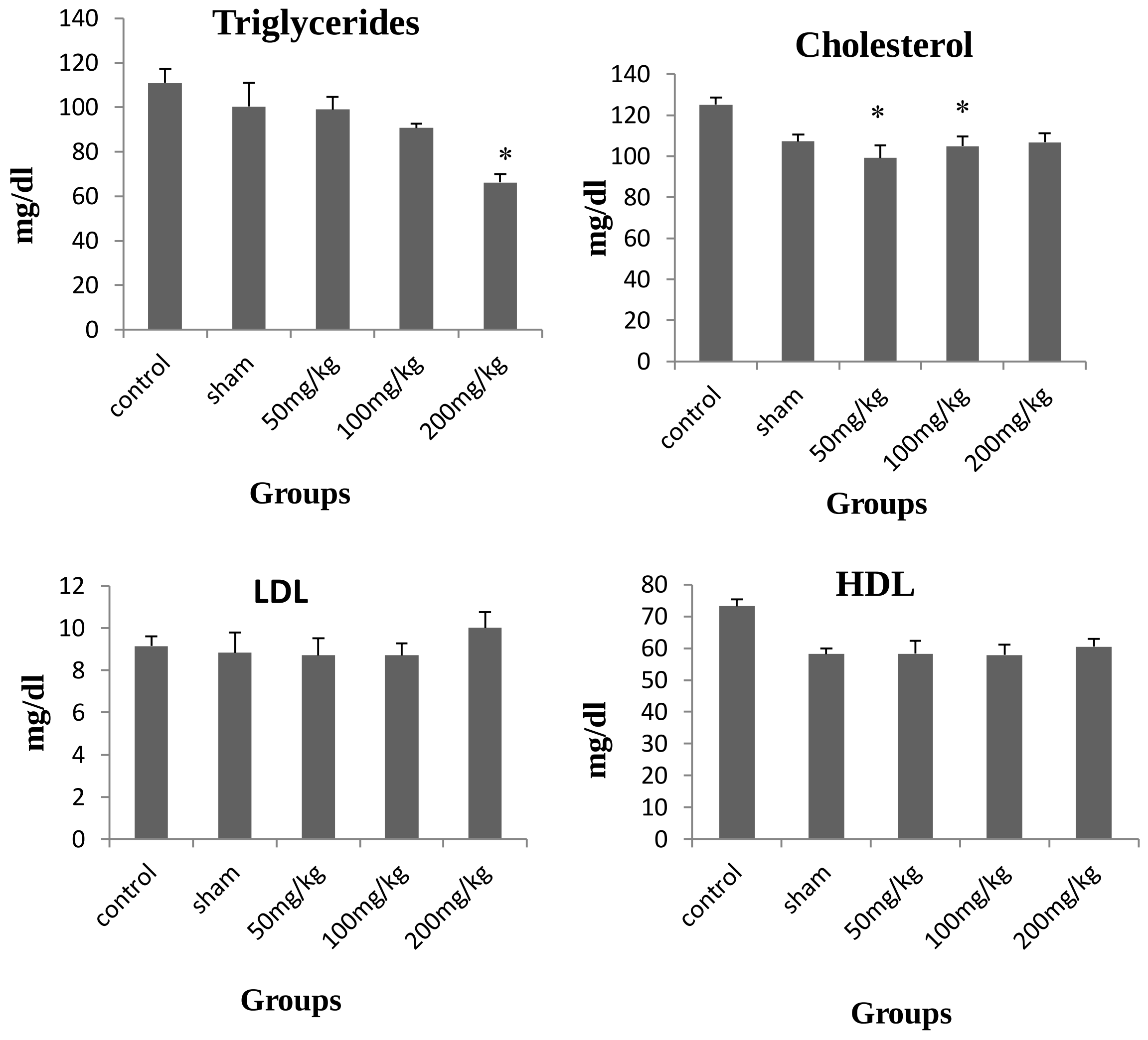

Fig. 2. The effect of fennel treatment on the serum lipid profile. Data are expressed as means ± SEM. *compared to control group ($P < 0.05$).

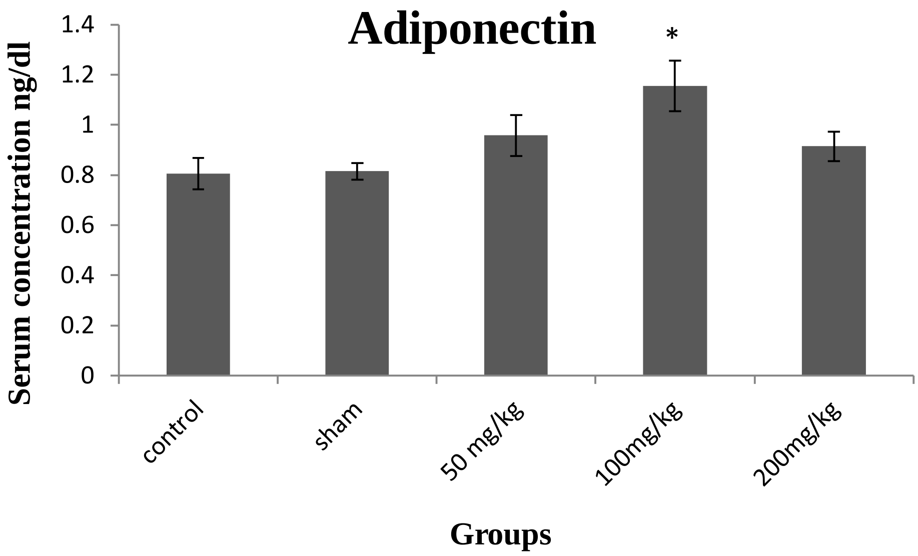

Fig. 3. The effect of fennel treatment on the serum adiponectin level. Data are expressed as means ± SEM. *compared to control group ($P < 0.05$).

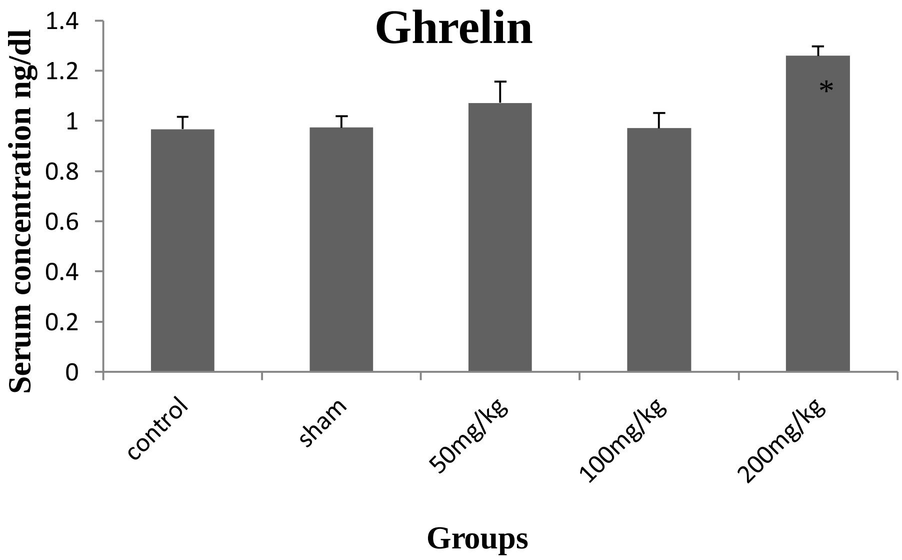

Fig. 4. The effect of fennel treatment on the serum Ghrelin level. Data are expressed as means ± SEM. *compared to control group ($P<0.05$).

- ***The impact of Funnel extract on the gene expression of Ghrelin and Adiponectin receptors***

This study suggests that the expression of the ghrelin receptor gene was reduced in all experimental groups compared to the control group, as shown in (Figure 5). The gene expression of the adiponectin receptor R2 was decreased in all experimental groups compared to the control group. No statistically significant differences in the adiponectin receptor R1 gene expression were observed among the different groups, as depicted in (Figure. 6).

The current investigation examined the potential impacts of aqueous extracts derived from fennel on various physiological parameters in BALB/c mice. Mainly, the study focused on body weight, serum lipid composition, ghrelin, and adiponectin levels, as well as the expression of their respective receptor genes. Based on the findings of this study, it can be inferred that the presence of fennel is significantly related to the reduction of serum cholesterol and triglyceride levels. The study's results noticed elevated plasma concentrations of ghrelin and adiponectin in certain dosage groups of fennel. Moreover, the findings of this study point to the decreased gene expression of the ghrelin and adiponectin receptor R2 under the influence of the fennel in all experimental groups.

Obesity is characterized by excessive adipose tissue accumulation, as supported by previous research (Cisternas *et al*., 2018). Adipokines, encompassing autocrine, paracrine, and endocrine factors, have been implicated in adipose tissue physiology (Trayhurn *et al*., 2006, Rosen and Spiegelman, 2014, Gupta *et al*., 2011). Adipokines, molecules secreted by adipose tissue, are crucial in maintaining homeostasis and regulating appetite signaling in the metabolic system (Laursen *et al*., 2017)

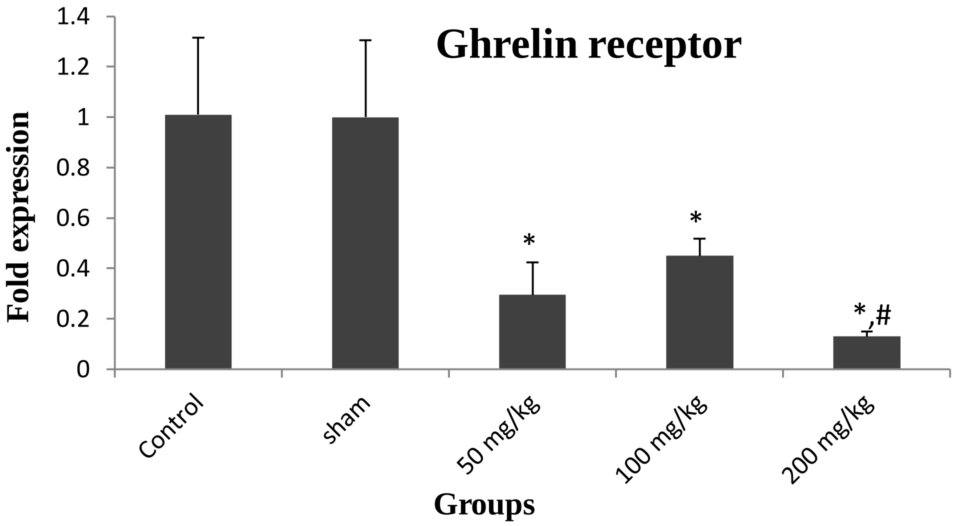

Fig. 5. The effect of fennel treatment on the Ghrelin receptor gene expression. Data are expressed as means ± SEM. *compared to control group. # compared to 100 mg/kg group (*P*<0.05).

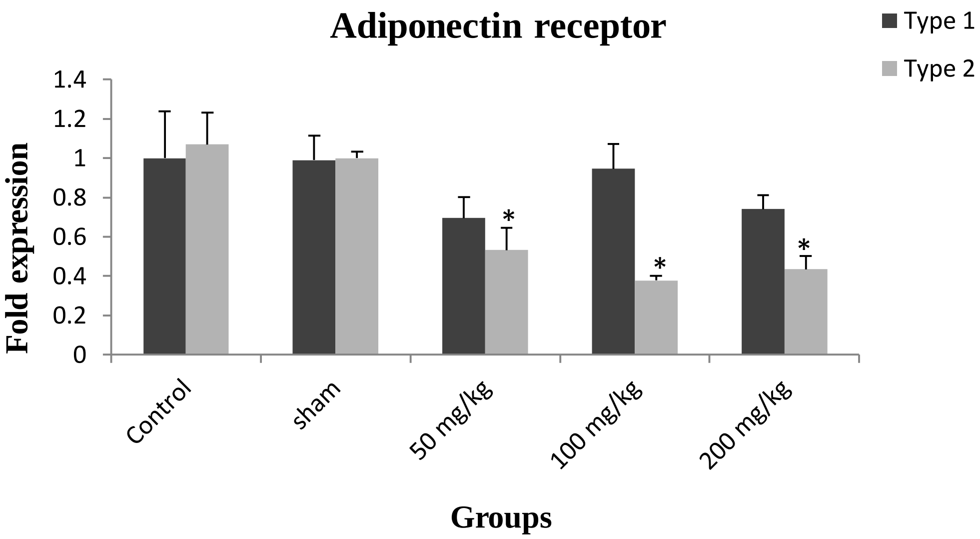

Fig. 6. The effect of fennel treatment on the adiponectin receptor gene expression. Data are expressed as means ± SEM. *compared to control group (*P* < 0.05).

Adiponectin is crucial in facilitating glucose uptake into skeletal muscle and liver while stimulating fatty acid oxidation within various tissues (Cho *et al*., 2016). Furthermore, it has been found that adiponectin catabolizes fatty acids in the periphery (Cisternas *et al*., 2018). In addition, the serum concentration of adiponectin exhibits an inverse relationship with insulin resistance and obesity, as indicated by previous studies (Chandran *et al*., 2003, Sowers, 2008, Yamauchi *et al*., 2001). Hence, a decrease in adiponectin levels is closely linked with an increased risk of obesity (Javanmardi *et al*., 2018). Adiponectin exerts its effects through the activation of both muscle-specific adiponectin receptor 1 (AdipoR1) and liver-specific adiponectin receptor 2 (AdipoR2) (Cho *et al*., 2016). Adiponectin has been found to enhance glucose utilization and beta-oxidation while inhibiting lipogenesis through its interaction with AdipoR2 and activation of AMPK (Wang *et al*., 2009). Besides, adiponectin has been shown to inhibit hepatic inflammation and fibrosis through its interaction with adipoR1 and AdipoR2 (Khaleel and Abdel-Aleem, 2018, Wang *et al*., 2009, Wulster-Radcliffe *et al*., 2004).

Ghrelin is synthesized and secreted from the gastric fundus. This orexigenic appetite-stimulating hormone could be considered an anti-obesity agent, as indicated by previous research (Lv *et al*., 2018). Administering ghrelin over an extended period increases body weight, as evidenced by previous research (Tschöp *et al*., 2000). Insulin and glucose are the components that exhibit a connection with ghrelin, a hormone known to exert inhibitory effects on meal termination (Doneda *et al*., 2015, Tschöp *et al*., 2001, English *et al*., 2002). Laursen *et al*. demonstrated that a reduction in adiponectin and ghrelin levels is associated with a concomitant decrease in appetite (Laursen *et al*., 2017). The capacity to manipulate these hormones has the potential to enhance the regulation of appetite. Alterations in the concentration of these hormones may induce a decrease in caloric consumption, leading to a more pronounced negative energy equilibrium, ultimately culminating in a subsequent decline in adipose tissue mass (Laursen *et al*., 2017).

Phytoestrogens are bioactive plant-derived compounds that exhibit certain similarities to estrogen in terms of their properties. The primary categories of phytoestrogens include isoflavones, lignans, flavonoids, and coumestans (Afiat *et al*., 2018). Foeniculum vulgare, commonly known as fennel, exhibits a high concentration of flavonoids, as supported by scientific literature (Prestwood *et al*., 2003). Research findings have indicated that the consumption of fennel, either in the form of tea or through aromatherapy, has the potential to reduce appetite among women who are overweight (Ghazanfarpour *et al*., 2018; Bae *et al*., 2015; Kim *et al*., 2005).

The study by Nejatbakhsh *et al*. demonstrated that the oral administration of fennel and cumin can reduce body weight. Cumin possesses a noteworthy abundance of phytosterols, which exhibit the ability to eliminate cholesterol from intestinal micelles, thereby reducing cholesterol absorption (Nejatbakhsh *et al*., 2017). According to the evidence, fennel has been found to regulate appetite, thereby potentially mitigating weight gain (Hur *et al*., 2006). The presence of trypsin inhibitors in fennel may lead to a decrease in food consumption and an increase in satiety by eliciting the release of cholecystokinin (Shahat *et al*., 2012). According to Galisteo *et al*. the decline in ghrelin synthesis resulted in reduced food consumption among obese rats administered Plantago seeds (Galisteo *et al*., 2005). Recent studies by Saleh *et al*. (2018) and Al-Sagon *et al*. (2020) discovered that adding fennel seed powder to broiler diets in amounts of 250, 500, and 750 g/50 kg and 1.2 and 3.2%, respectively, increased feed intake while the animals were under heat stress. Fennel seed (0.25 and 0.5%) was found to increase feed consumption when fed to broilers in a similar study by Saki *et al*. (2014).

According to Henda *et al*. (Mahmud, 2014) Japanese quails ate more feed when fennel seed was added to the diet (0.25, 0.50, and 0.75 g/kg). However, Bugdayci *et al*. (2018) discovered that fennel seed supplementation (0.3, 0.6, and 0.9%) had no impact on feed intake.

The enhanced palatability of the feed and the fennel's aroma can both be attributed to the rise in feed intake. By making the meal more palatable and raising the appetite of chickens, natural feed additives have positive effects for stimulating and activating the digestive system, resulting in greater feed intake (Khan *et al*., 2022). Additionally, the antibacterial and antifungal properties promote better nutrient digestion, leading to an increase in feed consumption (Hodgson *et al*., 1998). However, Soltan *et al*. (2008), Abou-Elkhair *et al*. (Ragab, 2007) and Zahira Abul-Jabbar *et al*. (2017) discovered that fennel powder (at doses of 0.25 to 1.5 g/kg, 1.0% and 2.5%, respectively) reduced feed consumption in broilers. Contrarily, Gharghani *et al*. (2015) discovered that adding fennel seeds to the diet (10 and 20 g/kg) had no impact on how much feed layers ate. The addition of fennel seed (100 to 400 ppm) to the diet of broilers had no impact on feed consumption, according to Safaei *et al*. (2020). The concentration of fennel active ingredients and their amount in the meal may be the cause of these inconsistent outcomes (Khan *et al*., 2022). In our investigation, we observed no statistically significant differences in the body weight of animals across various experimental groups.

In a study conducted by Helal *et al*. (2011) it was demonstrated that fennel possesses the potential to enhance hepatic lipid levels. The observed phenomenon can be attributed to the presence of an anti-oxidative property. According to Fatiha *et al*. it has been suggested that the methanol extract derived from fennel may possess potential anti-atherosclerotic and hyperlipidemic properties (Oulmouden *et al*., 2014). Jones *et al*. demonstrated that combining phytosterols with high-fat spreads significantly reduces cholesterol (St-Onge and Jones, 2003). The study conducted by Shahat *et al*. showed that the administration of Plantago seeds and fennel significantly decreased the lipid profile of obese rats. Specifically, it was observed that these interventions resulted in a notable reduction in LDL levels, commonly referred to as "bad cholesterol," while concurrently increasing the levels of HDL, often referred to as "good cholesterol." (Shahat *et al*., 2012). Collins *et al*. observed that the consumption of plant sterols resulted in elevated adiponectin levels, reduced body mass, and decreased LDL and cholesterol levels (Collins *et al*., 2007).

In a study by Tokede *et al*. (2015), it was found that those who consumed soy had significantly lower LDL, triglyceride, and total cholesterol levels. The use of different concentrations of fennel and savory essential oils, as well as their combination (0.15 and 0.25 g/kg), in the feed of broiler chickens improved the total cholesterol to high density lipoprotein (HDL) ratio, according to

Gharehsheikhlou *et al*. In developing quail, fennel (at doses of 0.25, 0.50, and 0.75 g/kg) resulted in a negligible increase in blood total protein, albumin, and globulin (Mahmud, 2014). Fennel extract (100 to 400 ppm) added to broiler feed showed no discernible impact on glucose, triglycerides, low-density lipoproteins (LDL), or triglyceride levels, whereas raising the amount of fennel extract in the meal increased HDL levels according to Safaei *et al*. (2020). Our research findings indicate a statistically significant decrease in cholesterol levels in the fennel groups administered 50 and 100 mg/kg doses. Furthermore, the group aided with a dosage of 200 mg/kg of fennel exhibited a substantial reduction in TG levels.

In this study, the level of ghrelin increased in the 200mg/kg. But level of adiponectin increased only in the 100 mg/kg. Interestingly the expression level of their receptors decreased in all treated groups. The fact that the increase in adiponectin expression was not dose-dependent, is related to various factors. According to previous studies, the concentration of fennel active and its ingredients may be the cause of these inconsistent outcome

Trans-anethole, a constituent of fennel, is renowned for its demonstrated effectiveness in appetite regulation (Bae *et al*., 2015). These molecules have been identified as biologically active compounds that exhibit estrogenic activity (Mahmoudi and Soleimani, 2013). Increased feed consumption in fennel supplemented birds may be caused by the presence of essential oil and active ingredients in fennel seed such as anethole and estragol, which stimulate the secretion of bile acid and digestive enzymes like protease, lipase, amylase, and maltase, which facilitate digestion (Platel and Srinivasan, 2001). It has been demonstrated that fennel seed (0.25, 0.50, and 0.75 g/kg) increases hunger, enhances endogenous digestive enzymes, and stimulates an immune response (Mahmud, 2014). The antibacterial and antibiotic properties of fennel, like those of other medicinal herbs, may help to lessen the number of undesirable intestinal microorganisms and enhance digestion (Elgayyar *et al*., 2001).

Additional research is warranted to enhance comprehension of the involvement of fennel and its constituent phytoestrogens in the modulation of energy homeostasis and adiposity. But there are some limits that must be understood. The most significant issues are those related to bioavailability, plant derivative metabolism, and the challenge of standardizing commercial products.

Conclusion

The findings of our study provide evidence for the efficacy of fennel extracts in modulating serum lipid profile. Fennel can elevate serum ghrelin and adiponectin levels in different dose, while reducing the expression of ghrelin and adiponectin receptor genes in the stomach and liver. More study is needed to better understand the role of fennel and its component in the obesity.

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