Original Article

Investigating the Impact of Caraway Extract on Metabolic Disorders in Male Rats with Induced Hypothyroidism

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Abstract

Background: Methimazole-induced hypothyroidism is a frequently used model for investigating thyroid dysfunction and the metabolic problems that accompany it. Conventional therapies, such as levothyroxine, are efficacious but might potentially cause adverse reactions. Caraway extract, derived from the Carum Carvi plant, is recognized for its antioxidant and anti-inflammatory characteristics. It has demonstrated promise in reducing these effects. **Objectives:** This study assesses its influence on thyroid hormone levels, weight gain, and blood glucose levels. **Materials and Methods:** Forty male Wistar rats were categorized into four groups. The control group (G1) did not receive any intervention or treatment. Group 2, referred to as the hypothyroid group, was intentionally administered methimazole to cause hypothyroidism. Group G3, referred to as the Caraway extract group, was administered caraway extract following the development of hypothyroidism. The positive control group (G4) was administered levothyroxine following the establishment of hypothyroidism. The diagnosis of hypothyroidism was confirmed by assessing reduced levels of free thyroxine (fT4) and free triiodothyronine (fT3), in addition to high thyroid-stimulating hormone (TSH). The efficacy of the treatments was assessed by comparing these metrics across the different groups. **Results:** The administration of caraway extract (G3) led to notable enhancements in thyroid hormone levels, characterized by increased concentrations of fT4 and fT3 and decreased levels of TSH compared to the hypothyroid group (G2). In addition, caraway extract effectively lowered blood glucose levels and facilitated weight gain, indicating improved metabolic health and glucose regulation. **Conclusions:** It could be concluded that caraway extract can successfully alleviate the effects of methimazole-induced hypothyroidism. These findings indicate that caraway extract may be a promising adjunct therapy for the management of hypothyroidism and associated metabolic problems.

Keyword: Antioxidant properties, Blood glucose levels, Caraway extract, Metabolic disorders, Methimazole-induced hypothyroidism, Thyroid hormones.

Introduction

Thyroid hormones are essential for regulating metabolism, growth, and development. This deficiency leads to various physiological disturbances, including significant effects on pancreatic function, body weight, glucose homeostasis, and insulin secretion [1]. Hypothyroidism is a common endocrine disorder characterized by insufficient production of thyroid hormones [2]. It is associated with decreased synthesis and the secretion of thyroid hormones (thyroxine (T4) and triiodothyronine (T3) and is characterized by a reduction in the serum level of thyroid hormones [3]. Hypothyroidism, according to its origin, can be divided into primary and secondary (central) types. Primary hypothyroidism occurs due to a disorder in the thyroid gland. Autoimmune thyroiditis, iodine deficiency, thyroidectomy, and the use of some particular drugs, such as thioamides, lithium, and iodine-containing drugs, can cause primary hypothyroidism [4]. The primary type is classified as either clinical hypothyroidism or subclinical hypothyroidism

[5]. Researchers have used antithyroid drugs, such as methimazole and propylthiouracil (PTU), to induce hypothyroidism in animal models [6]. Hypothyroidism is known to impair pancreatic beta-cell function, resulting in altered insulin secretion and glucose metabolism, which can lead to hyperglycemia and an increased risk of developing diabetes mellitus [7]. Additionally, hypothyroidism is associated with weight gain due to a reduced metabolic rate and alterations in lipid metabolism [8]. The relationship between thyroid dysfunction and glucose metabolism involves multiple pathways. Thyroid hormones influence insulin secretion and action, as well as glucose transport and metabolism in peripheral tissues [9]**.** Hypothyroidism can lead to decreased insulin sensitivity and impaired glucose utilization, contributing to insulin resistance [10]**.** Several studies have shown that administering some herbal drugs for the treatment of hypothyroidism [11], such as *Costus Pictus* leaf extract, Salvia officinalis, and wild pistachio oil, could improve the thyroid and TSH hormone levels in hypothyroid animals and that their herbal constituents, such as limonene and pinene, were responsible for these effects. Caraway *Carum Carvi,* a medicinal plant with a long history of use in traditional medicine, has been reported to possess various therapeutic properties, including antioxidant, anti-inflammatory, and antimicrobial activities [12]. Recent studies have suggested that caraway seeds may benefit thyroid function and metabolic processes. Caraway extracts have been shown to modulate thyroid hormone levels, improve lipid profiles, and enhance insulin sensitivity, making it a potential therapeutic agent for managing hypothyroidism and its associated metabolic disturbances [13]. The potential mechanisms by which caraway exerts its effects include bioactive compounds such as essential oils, flavonoids, and terpenes. These compounds have been shown to protect pancreatic beta-cells from damage [14]**.** Additionally, caraway has been reported to have lipid-lowering effects, which may benefit metabolic health [15]. This study aims to investigate the effect of caraway extract on metabolic parameters and hypothyroid disease in a rat model.

Materials and Methods

Forty male Wistar albino rats, ranging in age from 9 to 10 weeks and weighing 170 to 195 grams, were acquired from the Animal House of the College of Veterinary Medicine, University of Baghdad. The rats were regulated at 25°C, with a light/dark cycle of 12 hours each. The animals were randomly allocated to four cages.

- Control Group G1: (Negative Control): No treatment.
- Group G2: Induced hypothyroidism with methimazole (8 mg/kg of body weight) [16], no further treatment.
- Group G3: Induced hypothyroidism, treated with 400 mg/kg caraway extract daily for 28 days [17].
- Group G4 (Positive Control): Induced hypothyroidism, treated orally with levothyroxine 15ug/kg/day for 28 days [18].

Hypothyroidism was generated in the rats by orally administering a solution at a dosage of 8 mg per 100 g body weight once a day for 21 days. The volume of the solution given was 0.5 ml per 100 g body weight. Weekly measurements were taken for body weight and glucose levels. Hypothyroidism was definitively diagnosed after three weeks by testing the levels of T4 and TSH in the bloodstream. The duration of the treatment was 28 days. The caraway extract and levothyroxine were administered orally. Upon completion of the experiment, the

rats were administered ketamine and xylazine to induce anaesthesia. A cardiac puncture was performed to draw blood samples, which were then collected into gel tubes.

Caraway extracted Preparation

Sample Collection

The Caraway seeds were sourced from a nearby market in Babylon, Iraq. They were cleaned with an object immersed in a 5% sodium hypochlorite solution for 10 minutes, followed by three rinses with distilled water. The seeds were then dried in a shaded area at room temperature for 24 hours. After being dried, they were pulverized into fine powder using a Panasonic electric grinder [17].

Extract of Caraway

Fifty grams of ground dry caraway seeds were weighed and prepared using the aqueous-alcoholic extract. 500 ml of ethano alcohol with a concentration of 75% was added to this. The mixture was homogenized for 15 minutes and then moved to a hotplate magnetic stirrer for 48 hours at a temperature ranging from 45 to 50 degrees F. Following agitation, the mixture underwent centrifugation at a velocity of 3000 revolutions per minute for 30 minutes. The liquid component, the supernatant, was collected, while the solid residue, known as the sediment, was discarded. The technique was iterated three times to guarantee the thorough eradication of the silt. The obtained liquid was then filtered again using Whatman No.1 filter paper and dried using a water bath at a temperature of 60°C. The yield of the desiccated substance achieved from this procedure was 7.75 grams [31].

Sample Analysis

Gas chromatography-mass spectrometry (GC-MS) was utilized to evaluate the active components of the caraway extract. The GC-MS analysis was conducted using a Thermo Trace GC Ultra / TSQ Quantum GC-MS system with an Agilent HP-5ms Ultra Inert capillary column.

The measurement of biochemical parameters

Animal Weighing

Throughout the study, the rats' body weights were consistently assessed weekly to determine the medications' impact on their overall health and growth.

Glucose Concentration

According to the manufacturer's recommend-dations, a glucometer measured blood glucose levels weekly, so blood samples were collected from the tail vein.

Blood Collection

At the end of the experiment, cardiac punctures were used to extract blood samples from ten anesthetized animals in each group. Every rat underwent blood collection, which yielded roughly 1 ml of blood. The obtained blood was then allowed to clot and subjected to centrifugation at 3000 RPM for 10 minutes to separate the serum. The serum samples were preserved at -8°C until they were ready for further examination.

Hormonal Analysis

Per the manufacturer's instructions, serum values of thyroid-stimulating hormone, free thyroxine, and free triiodothyronine hormone were measured using ELISA kits (Cloud-Clone, USA).

Statistical Analysis

The data were analyzed using the Statistical Analysis System (SAS, 2018). Statistical significance was determined by assessing differences between groups using one-way and two-way ANOVA and the Least Significant Difference (LSD) test. A p-value less than 0.05 were deemed statistically significant [19, 20].

Ethical Approval

The study received ethical permission from the local animal care committee and was authorized for use at the College of Veterinary Medicine, University of Baghdad (approved number 1604,

26-7-2023). The operations involving animals were carried out under the guidelines for the care and utilization of laboratory animals.

Results

(GC/MS) that revealed 25 peaks corresponding to various components in the extract obtained through the aqueous-alcoholic (maceration) method, Figure 1. The primary compounds identified in the caraway extract included 3-0-glycosides, accounting for 22.9%, quercetin 3-glucuronide, 19.21%, and carvone, 5.06%, among other compounds, Table 1.

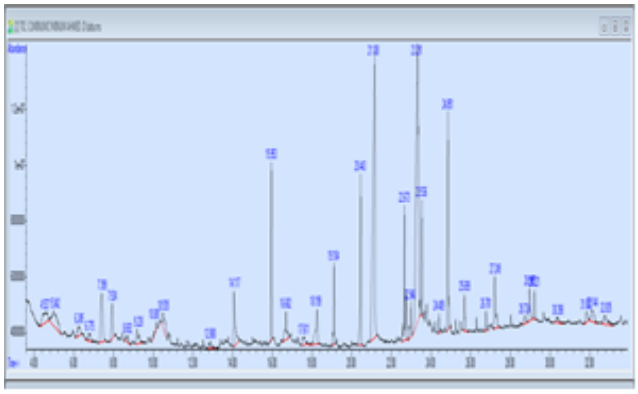

Figure 1: Gas chromatography-mass spectrometry (GC-MS) Analysis of Caraway extract

Table 1: Analysis of the Caraway extract phytochemical components using (GCMS).

Compounds	Retention time	Percentage area %
Butyl(dimethyl) silyloxypropane	4.53	1.82
Dimethylamine, N-(neopentyl oxy)	5.04	2.67
Quercetin, Kaempfero	6.24	0.89
Octanoic acid, methyl ester	6.77	0.61
palmitic acid	7.9	1.92
isoquercitrin, quercetin 3-0 caffeylglucoside, and kaempferol 3-glucoside	9.23	1.15
Propanoic acid, propyl ester	10.53	1.37
Benzoic acid,4-(1 methyl ethyl)-	12.88	0.59
1-Dodecanamine, N, N-dimethyl-Cetrimonium Bromide	14.12	2.71
4¢,5,7-trihydroxy-2¢-methoxy flavone	15.95	3.72
proteids and tannins	16.68	1.5
quercetin-3-glucuronides	18.19	2.38
2-methoxy-2-(4'-hydroxyphenyl) ethanol, junipediol A 2-O-beta-D-glucopyranoside and L-fucitol	20.43	4
quercetin 3-glucuronide isoquercitrine = quercetin-3-O-B-glucopyranoside quercetin-3-0-Caffeylglucoside kalmpferol-3-glucoside	21.105	19.21
3-0-glycosides	23.29	22.91
Carvone	24.85	5.7
linoleic acid	27.25	2.22
Alpha-terpinene	29.22	0.81
oleic acid	31.82	0.66
Limonene	32.83	1.06

Free Thyroxine (T4) Levels significantly differed among the groups (Figure 2). The group (G2) exhibited a significant decrease in levels compared to the control group; the (G3) and (G4) groups also significantly increased levels compared to the (G2) group. However, these levels remained lower than those in the control group.

The Thyroid-stimulating hormone (TSH) is significant across whole groups, as shown in (Figure 3). The group (G2) exhibited a substantial increase in TSH levels: The G3 and G4 groups showed a significant decrease in TSH levels.

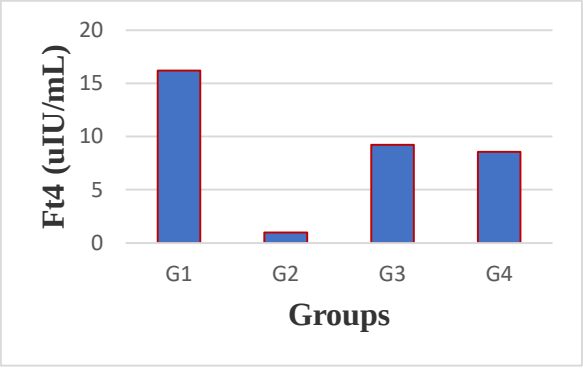

Figure 2: Effects of Caraway Extract and Methimazole-Induced Hypothyroidism on Thyroid Hormones in Male Wistar Rats.

Note:
*Different superscripts within the same column indicate significant differences ($p < 0.05$).
G1: Control group (without treatment).
G2: Induced hypothyroidism with methimazole, no further treatment.
G3: Induced hypothyroidism, treated with 400 mg/kg caraway extract daily for 28 days
G4 (Positive Control): Induced hypothyroidism, treated orally with levothyroxine 15ug/100g/day used for 28 days.

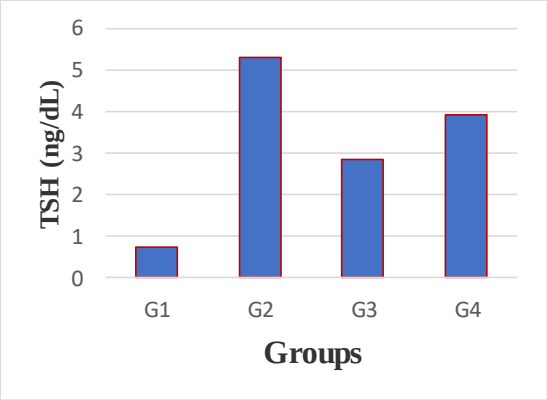

Figure 3: Effects of Caraway Extract and Methimazole-Induced Hypothyroidism on Thyroid Hormones in Male Wistar Rats.

Note:
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G1: Control group (without treatment).
G2: Induced hypothyroidism with methimazole, no further treatment.
G3: Induced hypothyroidism, treated with 400 mg/kg caraway extract daily for 28 days
G4 (Positive Control): Induced hypothyroidism, treated orally with levothyroxine 15ug/100g/day used for 28 days.

At the baseline, the groups had no notable disparities in glucose levels, as shown in (table 3). However, during the Induction period of 21 days, all induction groups showed significant increases in glucose levels in comparison to the control. In the seventh week, glucose levels were 109.20 ± 1.12 mg/dL for G3 and 106.20 ± 1.51 mg/dL for G4, significantly decreased ($P< 0.05$) to the G2 group 148.40 ± 1.42 mg/dL, with the control group remaining at 90.90 ± 1.21 mg/dL.

Table 2: Glucose concentration (mg/dL) in hypothyroidism with extracted treatment.

Time	G1	G2	G3	G4
Zero	A88.50±1.75**a**	A 91.40±1.27**f**	A90.10±1.04**f**	A92.20±1.48**f**
Induction period				
wk1	C90.20±1.39**a**	A106.90±1.93**e**	AB105.80±2.30**e**	B101.40±1.89**e**
wk2	C89.50±1.44**a**	AB122.30±1.37**d**	B120.10±1.46**bc**	AB123.30±2.40**b**
wk3	C91.40±1.64**a**	B127.70±1.87**c**	A135.30±1.85**a**	A136.20±2.82**a**
Treated period				
wk4	D92.90±1.14**a**	A140.60±2.50**b**	B123.70±2.04**b**	BC120.30±1.49**b**
wk5	D90.80±1.17**a**	A142.10±2.25**b**	B116.20±1.47**c**	B114.80±1.25**c**
wk6	D92.50±1.23**a**	A148.40±1.52**a**	B111.20±1.07**d**	B109.20±0.98**d**
wk7	D90.90±1.21**a**	A148.40±1.42**a**	B109.20±1.12**de**	BC106.20±1.51**d**
LSD	4.66			

Note:
- Values expressed as mean ± SE. n=5
- Dissimilar superscripts within a similar column and row designate significant differences ($p < 0.05$).
- At zero time, all groups show similar glucose levels with no significant differences.
- During the induction phase, significant increases in glucose levels are observed in G1, G2, and G3 compared to the control group from week 1 to week 3.
- In the treatment phase, glucose levels in G1 remain significantly higher than in other groups, indicating persistent hyperglycemia.
- Groups G2 and G3 show significant reductions in glucose levels by weeks 6 and 7 compared to the induction phase, suggesting the efficacy of the treatments.

Hypothyroidism has affected rats' weight gain, showing that caraway extracted treatment strongly influences weight gain. A significant variance was found between the beginning and the final body weights of the control and exploratory groups of rats, with a p-value of less than (P<0.01). Also, the groups that treated hypothyroidism G3 and G4 significantly increased ($P < 0.05$) in weight gain compared to the G2 shown in Table 4.

Table 3: Comparison of Initial and Final Average Body Weight (g) Among Groups in the Induction period.

Groups	Initial Mean ± S.D (n=10)	Induction Mean ± S.D (n=10) in day 21	Final Mean ± S.D (n=10)	Body weight gain (g)	P-value
G1	C 196.80 ± 2.23	B 256.60 ± 3.34 a	A 310.10 ± 9.82 a	105.30 ± 2.31 a	<0.01*
G2	C 191.20 ± 1.59	B 217.80 ± 2.10 c	A 242.90 ± 2.85 c	48.70 ± 3.10 c	
G3	C 190.50 ± 1.92	B 225.30 ± 2.11 bc	A 279.40 ± 2.39 b	87.40 ± 4.11 b	
G4	B 190.50 ± 2.08	A 227.90 ± 2.49 b	A 286.40 ± 2.51 b	91.20 ± 5.49 ab	

Note:

*Means with a different small letter in the same column are significantly different (P<0.05)

*Means with a different capital letter in the same row are significantly different (P<0.05).

G1: Control group (without treatment).

G2: Induced hypothyroidism with methimazole, no further treatment.

G3: Induced hypothyroidism, treated with 400 mg/kg caraway extract daily for 28 days.

G4 (Positive Control): Induced hypothyroidism, treated orally with levothyroxine 15ug/100g/day used for 28 days.

Discussion

This study examined the impact of caraway extract on thyroid hormone levels in male Wistar rats with methimazole-induced hypothyroidism. The induction group showed significantly reduced levels of both hormones, confirming the successful induction of hypothyroidism, which inhibits thyroid hormone production by blocking the thyroid peroxidase enzyme due to the effect of methimazole [21]. Administration of caraway extract significantly increased fT4 and fT3 levels compared to the hypothyroid group. The effectiveness of caraway extract can be attributed to its bioactive components, such as flavonoids and essential oils [22]. These chemicals can potentially safeguard thyroid tissue and facilitate the production of thyroid hormones. Nevertheless, the levels of fT4 and fT3 in these groups remained below those in the control group, suggesting that although caraway extract has therapeutic potential, it may not wholly restore thyroid function to normal levels. The notable decrease in TSH levels observed in the groups administered caraway extract (T2) and levothyroxine (T3) suggests an enhancement in thyroid function. This phenomenon may be attributed to the improved transportation of the bioactive components of caraway, which could effectively promote the synthesis and release of thyroid hormones [23].

Levothyroxine, a synthetic form of thyroxine, is a typical treatment used for hypothyroidism. It effectively restored thyroid hormone points and reduced TSH stages [24]. However, caraway treatments showed comparable improvements, indicating their potential as alternative or complementary therapies. [25].

Thyroid hormones are crucial in regulating metabolic processes, including glucose homeostasis. Decreased basal metabolic rate (BMR), reduced energy expenditure, and weight gain can lead to several metabolic disturbances, exacerbating insulin resistance [26] [27].

Caraway (*Carum Carvi*) has been typically used for its medicinal properties, particularly in digestive and metabolic disorders. The tonic effects of caraway extract on hypothyroidism and glucose levels are attributed to its bioactive compounds, such as carvone, limonene, flavonoids, and polyphenols [28], improve insulin sensitivity and glucose uptake by tissues, helping to lower blood glucose levels [29].

Hypothyroid rats experienced a significant weight reduction compared to normal rats. Notably, there was a non-significant difference in food and water intake among the control and experimental groups. On the other hand, according to education on humans, reasonable increases in TSH levels were linked with a significant decrease in men's weight gain [30]. The results demonstrated significant changes in body weight among the different treatment groups, highlighting the potential benefits of caraway-based therapies in managing hypothyroidism and associated metabolic

disturbances [32]. Rats given caraway extract significantly improved weight gain compared to the induction group.

Conclusion

The study demonstrated that caraway extract significantly improves thyroid hormone levels, glucose metabolism, and weight gain in male rats with methimazole-induced hypothyroidism. Caraway extracts augment thyroid hormone levels while reducing thyroid-stimulating hormone levels. Moreover, it lowers blood glucose levels and recovers weight growth, probably attributable to its antioxidant and anti-inflammatory capability.

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Conflicts of interest

There are no conflicts of interest.

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