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EFFECTIVENESS OF *ANETHUM GRAVEOLENS L.* ON ANTIOXIDANT STATUS, THYROID FUNCTION AND HISTOPATHOLOGY

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Abstract

Context. *Anethum graveolens L.* is used in the treatment of numerous diseases. But there is limited data about the *Anethum graveolens* efficiency in thyroid tissue.

Objective. The aim of this study is to assess the functional and histopathological changes in thyroid tissues from rats treated with *Anethum graveolens L.* extract.

Design. This is an experimental animal study and duration of the study was 30 days.

Subjects and Methods. Twenty-eight female Wistar Albino rats were divided into four equal groups. A gavage of *Anethum graveolens L.* extract at 0, 50, 150 and 300 mg/kg/day doses were given to the rats with 1 mL 0.9% NaCl, respectively, for 30 days. Blood was taken at day 0, 15 and 30. fT3, fT4, TSH values and antioxidant efficiency were observed. Also the thyroidectomy tissue was assessed histopathologically.

Results. There is no difference observed in the fT3, fT4 and TSH values of groups 1, 2 and 3 at day 1, 15 and 30 ($p>0.05$); however, in group 4, TSH value decreased on days 15 and 30 when compared to day 1 and the other groups ($p<0.05$). Also the hypertrophy and thyroid follicular cell hyperplasia were significantly increased in group 4 ($p<0.05$). There is no difference in antioxidant efficiency in any of the groups ($p>0.05$).

Conclusion. *Anethum graveolens L.* extract is effective on both the function and the histology of thyroid tissue but it has no effect on antioxidant status.

Key words: *Anethum graveolens L*, thyroid, antioxidant, histopathology, rat.

INTRODUCTION

Dill (*Anethum graveolens L.*) locally named "dereotu", is a member of the Apiaceae family, and grows mostly in the Mediterranean Region, Europe, central and south Asia, and southeastern Iran (1). The dill seed and its leaves are used as a flavoring in sauces, vinegar, salads, soups and various meals (2,3).

Thyroid diseases have a significant place amongst the endocrine diseases and thyroidectomy is the most frequently performed endocrine surgery (4). There are also some medical treatment options for the treatment of hyperthyroidism and hypothyroidism. In the Eastern world, alternative treatment methods for most diseases are well established (5). Herbal alternative management used in the treatment of various diseases, such as diabetes and thyroid diseases, has become widespread throughout the world over time; however, studies are still being performed to assess these treatment methods (5,6).

Anethum graveolens L. is used in the treatment of numerous diseases. It has been used as an alternative method in the treatment of flatulence, indigestion, stomach pain and other various disorders (7). There are also studies regarding the hypolipidemic, antimicrobial and infertility preventing effects of *Anethum graveolens L* (8-10). Despite *Anethum graveolens L.* has been used in traditional medicine for the treatment of thyroid diseases, we observed only one experimental study regarding the efficiency of *Anethum graveolens L.* on thyroidal diseases. In this experimental study that was investigating *Anethum graveolens L.*'s potential effect in Diabetes Mellitus (DM) regulation, T3 and T4 values were also examined, but there is no data regarding the goiter progression (2).

In this study, the functional and histopathological changes in the normal thyroid tissue from rats which applied *Anethum graveolens L.* extract via gavage are investigated because of its possible uses of *Anethum graveolens L.* on goiter patients in the future.

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MATERIAL AND METHODS

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The study protocol was approved by the Local Animal Ethical Committee. Throughout the experiment, the animals were kept/held in standard cages. The animals were fed with pellet-type feed produced specifically for small experimental animals. The animals were in a room with a 12-hour light/ 12-hour dark cycle. Twenty-eight female Wistar Albino rats (median weight: 275 g, median age: 4.5 months) were divided into four equal groups.

Preparation of the *Anethum graveolens L.* extract: The aerial parts of *Anethum graveolens L.* consisted of stems and leaves were purchased from the local markets in the amount of 3 Kg. The purchased plants were identified at Bezmialem Vakif University, Faculty of Pharmacy, Department of Pharmaceutical Botany comparing with "Flora of Turkey and the East Aegean Islands" (11). A voucher specimen was kept in Bezmialem Vakif University herbarium. The plant materials were dried in shadow and powdered. The powdered plants were extracted in 2 L of ethanol at room temperature twice for three days. The extract was filtered and evaporated under vacuum. Thirty-two grams of ethanol extract was obtained. The extract was frozen at -85°C overnight and freeze-dried for 24 hours. Three different dosages of the completely dried ethanolic extract consisting of 50, 150 and 300 mg/kg (whole animal body weight) were prepared using water and 0.05% Tween 80. The mixture obtained was utilized for application via gavage.

Rats in the first group (n=7) were the control group, and only 1 mL 0.9 % NaCl were administered as vehicle solution. *Anethum graveolens L.* extract at 50, 150 and 300 mg/kg/day doses, respectively, were given to the rats in the second (n=7), third (n=7) and fourth (n=7) groups by gavage in 1 mL 0.9 % NaCl for 30 days. Blood was taken from all of the rats before and on day 15 and 30 post- *Anethum graveolens L.* extract application, and free T3 (pmol/L), free T4 (pmol/L) and thyroid-stimulating hormone (TSH) (mIU/L) values were assessed by rat ELISA kits (Rat TSH, Free T3, T4 ELISA kits, EIAAB®, Wuhan, China). Serum paraoxonase status (PON) (U/L), total oxidant status (TOS) (μmol H_2O_2 Eq/L), and serum arylesterase status (ARES) (KU/L) (CliniSciences, Nanterre, France) values were assessed from the blood taken on days 1 and 30.

General anesthesia was applied to all of the rats after they were fed with the *Anethum graveolens L.* extract for 30 days. The anterior neck was shaved and sterilized with a povidone-iodine solution (Batticon® 10 g povidone-iodine, Adeka Ilaç, Istanbul, Turkey). Following a 2 cm longitudinal incision in the anterior neck area, the submaxillary tissues and muscles were retracted laterally, and the trachea, as well as the bi-lobular thyroid tissues on both sides, were visualized. A bilateral subtotal thyroidectomy was performed. The rats were then sacrificed after obtaining 3 mL of blood through the intracardiac entry.

Histopathological Evaluation

The resected tissues were fixed in formaldehyde. Cross cuts of 5 μm were stained first with hematoxylin and eosin and then with collagen stain. The evaluation was conducted with a light microscope at 100x magnification. The evaluation was made by a pathologist (who was blinded regarding the group assignments) according to the "histopathological atrophy/ hypertrophy schemes" (Tables 1-4) (12).

Statistical Analysis

The statistical analyses were conducted using the SPSS 21.00 package software. Group values of fT3, fT4, and TSH were evaluated by one-way ANOVA test between themselves and between the groups. Antioxidant parameters were also evaluated by one-way ANOVA test between the groups. To find the source of the difference between the groups, the Post Hoc Tukey's HSD test was applied. The comparison of histopathological intergroup scores was made using The Kruskal Wallis test. To determine which two groups produce an intergroup difference, the Post Hoc Dunn test was used. The results were evaluated at the $p<0.05$ significance level.

Table 1. The severity grading scheme for thyroid gland hypertrophy

Grade	Descriptor	Criteria
0	Non-remarkable	Less than 20% enlargement of glands in comparison to the controls.
1	Mild	Diffuse enlargement of gland that exceeds the control size by 30-50%
2	Moderate	Diffuse enlargement of gland that exceeds the control size by 60-80%
3	Severe	Diffuse enlargement of gland that exceeds the control size by greater than 80%. There is contact of both lobes at the midline and they exceed normal boundaries into the surrounding tissue space.

Table 2. The severity grading scheme for thyroid gland atrophy

Grade	Descriptor	Criteria
0	Non-remarkable	Less than a 20% reduction in size in comparison to control
1	Mild	Gland size is 30-50% reduced in comparison to control
2	Moderate	Gland size is 60-80% reduced in comparison to control
3	Severe	Gland size is > 80% reduced in comparison to control

Table 3. The severity grading scheme for follicular cell hypertrophy

Grade	Descriptor	Criteria
0	Non-remarkable	Fewer than 20% of the cells exhibit hypertrophy
1	Mild	30-50% of follicular cells exhibit hypertrophy
2	Moderate	60-80% of follicular cells exhibit hypertrophy
3	Severe	Over 80% of follicular cells exhibit hypertrophy

Table 4. The severity grading scheme for follicular cell hyperplasia

Grade	Descriptor	Criteria
0	Non-remarkable	Focal or diffuse crowding of follicular cells affecting less than 20% of the tissue.
1	Mild	Focal or diffuse crowding of follicular cells affecting less than 30-50% of the tissue, and/or single or multiple papillary infoldings of the follicular cell layer.
2	Moderate	60-80% of the follicles exhibit focal hyperplasia characterized by pseudostratified or stratified follicular epithelium. Papillary infolding may be present.
3	Severe	Over 80% of the follicles exhibit extensive hyperplasia with stratification of 2-3 cell layers thick. Papillary infolding may be present.

RESULTS

There are no differences in the values of fT3, fT4 and TSH from blood taken on days 1, 15 and 30 in groups 1, 2 and 3. ($p>0.05$); however, in group 4, TSH value decreased on days 15 and 30 compared to day 1 ($p<0.05$) (Table 5).

An intergroup difference was found in the TSH value from the blood taken on day 30 ($p<0.05$) (Table 5). Upon further analysis, we observed that the intergroup difference originated from the difference between group 2 and group 4. Also, the TSH levels decreased with dose increment even if there are no significant differences between the groups. Moreover, although there is no difference between the fT3 and fT4 values, fT3 and fT4 decreases are remarkable in group 4 which received high doses of *Anethum graveolens L.*

No difference was found in the antioxidant efficiency (PON, TOS, ARES) of the *Anethum graveolens L.* extract between the groups upon the assessment of the blood taken on days 1 and 30 ($p>0.05$) (Table 6).

A histopathological difference in the thyroidectomy materials was assessed based on the presence of atrophy, follicular cell hypertrophy and follicular cell hyperplasia. We observed a difference in hypertrophy and follicular cell hyperplasia. To determine from which groups this difference originated, Post Hoc Dunn test was performed; the

Table 5. The statistical analysis of fT3, fT4 and TSH values of days 1, 15 and 30 in each group and between the groups

	Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	Group 4 Mean ± SD	p value (One-way ANOVA test)
TSH day 1 (mIU/L)	11.31 ± 4.09	12.51 ± 6.98	9.60 ± 4.44	8.14 ± 2.70	0.362
TSH day 15 (mIU/L)	10.55 ± 4.14	10.1 ± 6.36	13.74 ± 11.13	4.69 ± 1.72	0.122
TSH day 30 (mIU/L)	6.47 ± 3.32	11.16 ± 5.37	7.35 ± 4.03	4.36 ± 1.49	0.021
p value (one-way ANOVA test)	0.067	0.773	0.277	0.005	
fT3 day 1 (pmol/L)	9.09 ± 4.16	12.3 ± 8.49	11.98 ± 7.05	6.59 ± 4.62	0.311
fT3 day 15 (pmol/L)	9.64 ± 5.22	7.7 ± 5	9.63 ± 5.99	4.05 ± 0.8	0.147
fT3 day 30 (pmol/L)	6.33 ± 2.71	8.82 ± 5.14	6.76 ± 3.37	4.47 ± 0.01	0.201
p value (one-way ANOVA test)	0.302	0.397	0.255	0.314	
fT4 day 1 (pmol/L)	46.21 ± 15.83	54.02 ± 31.56	55.09 ± 33.55	41.29 ± 27.81	0.766
fT4 day 15 (pmol/L)	46.97 ± 17.3	42.62 ± 16.94	52.9 ± 29.86	26.44 ± 3.18	0.091
fT4 day 30 (pmol/L)	35.92 ± 16.11	38.34 ± 22.61	29.83 ± 10	25.56 ± 4.44	0.386
p value (one-way ANOVA test)	0.390	0.478	0.172	0.159	

difference in both hypertrophy and follicular cell hyperplasia originated from the difference between groups 1 and 4 (Table 7, Fig. 1). Group 4 which was treated with high doses of *Anethum graveolens L.* had more hypertrophy and follicular cell hyperplasia, despite that the control group which is named as group 1 had lower hypertrophy and follicular cell hyperplasia.

DISCUSSION

Anethum graveolens L. has been used for a long time in the treatment of many diseases, particularly in alternative medicine (13). Moreover, *Anethum graveolens L.*'s anti-inflammatory (14), antimicrobial (15) or antibacterial (16), antihyperlipidemic, antihypercholesterolemic (8), antioxidative (17) and blood glucose reducing (18) effects were found

Table 6. The statistical analysis of the anti-oxidative parameters between the groups

	Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	Group 4 Mean ± SD	p value (one-way ANOVA test)
PON day 1 (U/L)	453.56 ± 118.82	498.36 ± 89.36	542.91 ± 63.42	509.45 ± 71.81	0.327
PON day 30 (U/L)	417.85 ± 89.16	327.99 ± 63.20	355.51 ± 86.22	286.31 ± 137.87	0.138
TOS day 1 (μmol H_2O_2 Eq/L)	5.96 ± 0.68	5.33 ± 0.48	5.19 ± 0.70	5.57 ± 0.73	0.229
TOS day 30 (μmol H_2O_2 Eq/L)	3.84 ± 0.27	7.51 ± 6.55	3.36 ± 0.46	9.21 ± 11.75	0.346
ARES day 1 (KU/L)	406.50 ± 18.15	390.31 ± 17.19	396.66 ± 26.76	395.25 ± 40.81	0.828
ARES day 30 (KU/L)	304.19 ± 28.82	308 ± 42.67	290.98 ± 38.48	291.49 ± 58.29	0.837

Table 7. The statistical analysis of the histopathological examination of hypertrophy and follicular cell hyperplasia

		Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)	p value Kruskal-Wallis test
Hypertrophy	Grade 0	14.28	42.85	0	0	0.005
	Grade 1	85.72	57.15	71.42	28.57	
	Grade 2	0	0	0	28.57	
	Grade 3	0	0	28.58	42.86	
Follicular cell hyperplasia	Grade 0	85.72	57.15	28.58	0	0.010
	Grade 1	14.28	42.85	71.42	100	
	Grade 2	0	0	0	0	
	Grade 3	0	0	0	0	

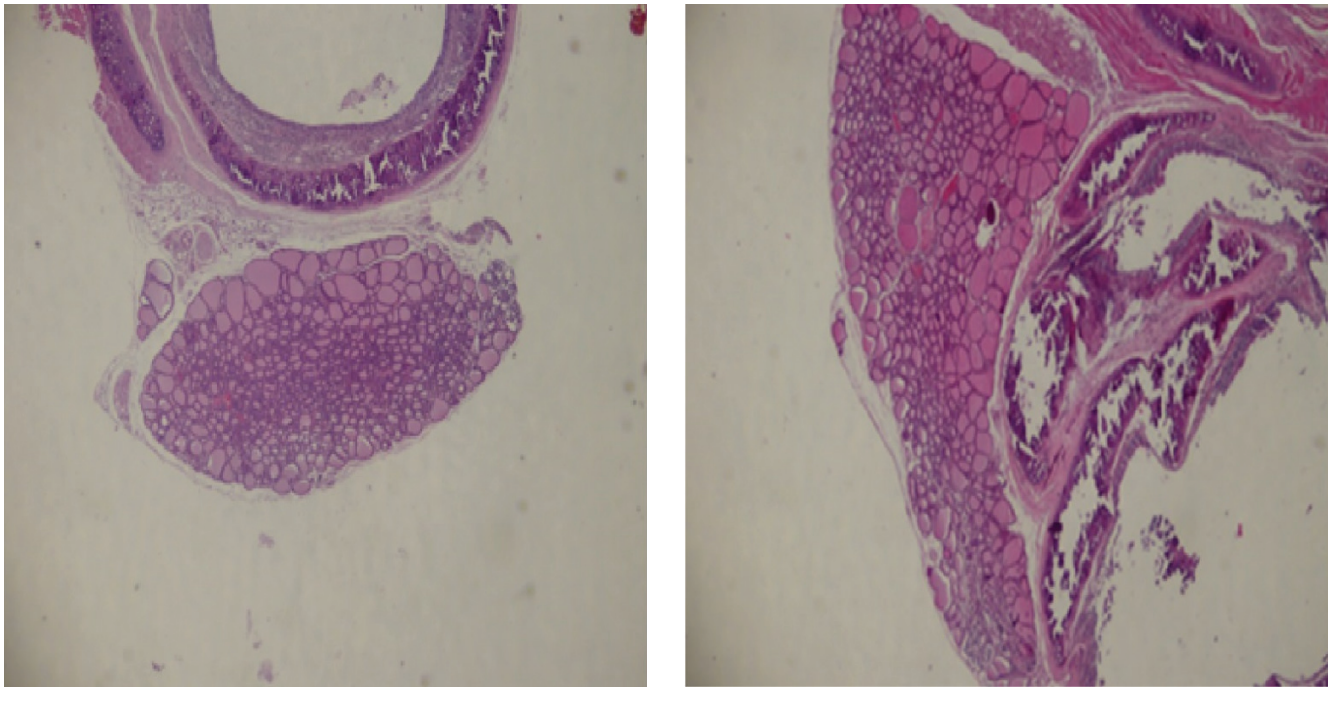

Figure 1. Grade 0 follicular cell hyperplasia in group 1 (a) and Grade 1 follicular cell hyperplasia in group 4 (b).

pharmacologically. There are several studies on herbal treatments that are used in thyroid diseases. In a study by Lee *et al*., the clinical effect of the Ahnjeonbaekho-tang plant was tested on 22 patients who experienced side effects in relation to anti-thyroid medications for Graves' disease, which is an autoimmune thyroid disease. Serum T3 and T4 levels decreased and serum TSH levels increased in the patients treated with this plant (6).

Anethum graveolens L. is rich in tannins, terpenoids, flavonoids, and cardiac glycosides (19). Flavonoids, commonly found in herbal-based foods, have several biological activities such as antioxidant (20) and antithyroid effects (21, 22). The consumption of flavonoids and other xenobiotics by experimental animals causes an expansion and histological change in the thyroid gland, and a reduction in iodine uptake and TPO activity (21, 23). Previous studies have reported the anti-thyroid activity of the flavonoids, but no studies determined the direct effect of *Anethum graveolens L.* on thyroid hormones. In a study by Panda *et al*., the effect of *Anethum graveolens L* on DM regulation and thyroid function were examined. The results showed that T3 and T4 values were higher in the group that received *Anethum graveolens L.* However, there was no potential explanation for these results (2).

In our study, there was no significant difference in the T3 and T4 levels of the groups that were and were not given *Anethum graveolens L.* extract. However, there was a significant decrease in the TSH level in the group that received 300 mg/kg *Anethum graveolens L.* extract when compared to the other groups on day 30. This could suggest that *Anethum graveolens L.* could be useful for hyperthyroidism at high doses.

Publications in the literature are lacking on the histopathological effects of *Anethum graveolens L.* on the thyroid tissue. In a study on the effects of *Anethum graveolens L.* on the male reproductive system, the *Anethum graveolens L.* extract did not cause any change in the sperm concentration, acrosome reaction, or the testis and epididymis histopathology (24). During the histopathological evaluation, we observed a significant difference in the presence of hypertrophy and follicular cell hyperplasia but there is no data to support our finding to correlate with the literature.

In a study that evaluated the hypolipidemic and antioxidant activity of *Anethum graveolens L.* in rats with acetaminophen-induced liver damage, 28 rats were analyzed upon being divided into four equal groups. The first group served as the control group and did not undergo any operation; the other three groups were given 2 g/kg paracetamol by gastric tubes to create liver damage. The second group did not receive any additional treatments; the third and fourth groups were given *Anethum graveolens L.* powder (10% of *Anethum graveolens L.* powder in the diet) and *Anethum graveolens L.* extract 300 mg/kg by gavage, respectively. After 45 days, there was liver damage in both of the treated groups; liver function enzymes and certain lipid parameters significantly decreased when compared to the untreated group. On the other hand, glutathione peroxidase and superoxide dismutase enzymes significantly increased. The authors suggested that these results depended on *Anethum graveolens L.*'s antioxidant property (25). In a study by Bahramikia *et al*., who measured the antioxidant effectiveness of *Anethum graveolens L.*, rats were divided into five groups; the first group served as the healthy control group, and the other groups were made hypercholesterolemic through the feeding of a high-fat diet for three weeks. Then, three groups were treated with different fractions of *Anethum graveolens L.* extract for two weeks (50 mg/kg/day) and a significant decrease was found in the total cholesterol, low-density lipoprotein (LDL), and triglyceride levels of these groups. The study found that lipid peroxidation decreased in rats that were fed a high-fat diet and that the *Anethum graveolens L.* treatment significantly increased hepatic antioxidant system activities, such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) (26). In the current study, no significant difference was found in the antioxidant proteins between the groups, unlike the literature. The possible reason for that is that we used only *Anethum graveolens L.* and there is no confounding factor for our study, but in the other studies the animals had an operation or diet interventions and this could affect the results.

In conclusion, the results obtained here show that the *Anethum graveolens L.* extract has effects on both the function and the histology of thyroid tissue. *Anethum graveolens L.* can affect the thyroid functions like as hypothyroidic effect at high doses by changing the TSH values and the TSH decrease is considerable at the longer time period. Also, the *Anethum graveolens L.* had more hypertrophy and follicular cell hyperplasia in higher doses and this could be useful for hyperthyroidism in the near future but there is a need for prospective randomized human trials for future evaluations.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical approval

All institutional and national guidelines for the care and use of laboratory animals were followed.

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