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Research Article

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Animals in Levothyroxine Model of Thyroid Damage Are Positively Affected by the Consumption of *Descurainia sophia L.* Extract (Brassicaceae)

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Abstract

There are some promising bioactivities related to Brassicaceae plants, including chemoprotective and anti-cancer effects, through various mechanisms which are mainly related to the number of phytochemicals such as glucosinolates and their hydrolysis products, isothiocyanates. The dietary intake of glucosinolate constituents, which are dominant in Brassicaceae plants, has been shown to interfere with the thyroid gland's iodine uptake and metabolism through competitive inhibition. *Descurainia sophia L.* (*D. sophia*) seeds, commonly named Khakshee, possess a great amount of gluconapin, a glucosinolate known for its goitrogenic properties, which potentially may have protective effects on thyroid dysfunctions. The present study evaluated the possible ameliorative activities of hydroalcoholic extract from *D. sophia* seeds in regulating hyperthyroidism in a levothyroxine-induced rat model. The 70% hot methanol extract from the plant seeds was prepared using the maceration method, and the total glucosinolate content was determined using UV spectrophotometry. The serum thyroid hormone levels and histopathological features of the thyroid gland were assessed to evaluate the protective effects of extract in hyperthyroidism induced by injection of levothyroxine in rats. The administration of the extract by oral route has been associated with a significant decrease in the levels of FT4 and FT3. Further, the treatment group showed a notable reduction in TSH levels. The histopathological findings showed that the consumption of extract attenuated the adverse effects of levothyroxine. Spectrophotometric analysis revealed the presence of glucosinolates in the extract, which was calculated at 24.14 ± 0.8 mmol equivalent of sinigrin per kilogram of dried seeds. Based on the results of this study, it appears that glucosinolates are responsible for protecting *D. sophia* against levothyroxine-induced thyroid damage in rats. While Brassicaceae plants are recognized for their potential health benefits, particularly in reducing the risk of various diseases, including cancer, limiting the consumption of certain species, such as Khakshee, is important due to the possibility of affecting thyroid hormone levels by these plants.

Keywords: *Descurainia sophia L.*; Extract; Glucosinolate; Hyperthyroidism; Levothyroxine; Methimazole.

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1. Introduction

Descurainia sophia L. Webb ex Prantl is a weedy plant belonging to the Brassicaceae family. The plant is commonly distributed worldwide, including in Asia, and grows in most parts of Iran [1]. Based on Iranian traditional medicine texts, this plant is called Todri, Khakshee, Khaksheer, or Khobbah and is used for medicinal purposes [2]. Traditionally, *D. sophia* seeds are purgative and astringent and are used to relieve cough inflammations and reduce edema [1, 3]. Several phytochemical investigations on *D. sophia* resulted in the isolation of several biological compounds, including phenolics (flavonoid and coumarin), fatty acids, lipids, steroids, and glucosinolate (GSL) [4-7]. The Brassicaceae plants have been shown to exert several potential bio-protective effects, including anticarcinogenic, chemoprotective, and bio-fumigant and bioprotective effects mainly related to their glucosinolate constituents [8, 9]. The underlying mechanisms of action associated with Brassicaceae species can be listed as:

Enhancement of Phase 2 Enzymes by increasing the activity of phase 2 detoxification enzymes, including glutathione S-transferase (GST), UDP-glucuronosyltransferase, and quinone reductase, reduction of lipid peroxidation, affecting the release of pro-inflammatory cytokines for controlling inflammation-related conditions, gene expression alterations and hormonal modulation. Due to the above beneficial effects on human health, different Brassicaceae species have garnered significant attention in recent years [9].

Structurally, glucosinolates (GSLs) contain sulfur and nitrogen atoms found in leaves, stems, roots, and mainly seeds of plants belonging to Brassicaceae. The hydrolysis of GSLs by myrosinase, along with intestinal microflora and thermal degradation activity, leads to the formation of unstable intermediates. These intermediates subsequently convert into various products, including isothiocyanates, nitriles, and thiocyanates. [10]. Recent studies indicate that consuming glucosinolate-containing meals can interfere with thyroid iodine uptake in mammals, reducing serum levels of free thyroid hormones, specifically FT3 and FT4. This interference increases the secretion of thyroid-stimulating hormone (TSH), which subsequently causes hyperactivity of the thyroid follicles and hypertrophy of thyroid tissue [11, 12]. It was previously shown that the intake of some Brassicaceae species, such as *Brassica napus* sprouts, by animals with hypothyroidism can alleviate the resulting adverse effects without harming healthy animals [13].

The present study was designed for investigation of the activities of 70 % hot methanol (70 °c) extract from *Descurainia sophia* seeds against hyperthyroidism induced by levothyroxine (LT4) in rats by assessment of serum thyroid hormone levels and histological analysis of the thyroid gland. Moreover, the total amount of glucosinolate in the extract was measured by Ultraviolet-visible (UV) spectroscopy.

2. Materials And Methods

2.1. Extract preparation

D. sophia seeds were purchased from the traditional market of Sari, Iran. The voucher specimen (E1-26-261) was deposited in the Herbarium of the Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran. The sample was dried and ground to a fine powder. The powder was mixed with 70 % methanol at 70 °c (to deactivate myrosinase in the seed tissue) and soaked for 24 h at room temperature [14]. The extract was concentrated using a rotary evaporator, and the dried material was freeze-dried for 24h and stored at -20 °C. The extract yield was estimated at 2.932% (w/w).

2.2. Total glucosinolates analysis

The total glucosinolate concentration in *D. sophia* extract was measured based on the method explained by Jezek et al. [15]. Based on this method, the alkaline treatment of GSLs in the extract produces 1-thioglucose. This compound can react with ferricyanide to reduce. Finally, the absorbance of the extract and standard solutions were measured using a spectrophotometer at 420 nm. Different concentrations (0–1 mg/mL) of sinigrin were used for plotting the standard curve [8].

2.3. Animals

The Wistar rats (Female, 180-185 g) were received from the Animal Research Center of Mazandaran University of Medical Sciences, Sari, Iran, and kept under standard conditions. Animals were adapted to the laboratory room a week before the beginning of the experiment and hosed in the cages under 12 h light and dark cycles, keeping at

room temperature with humidity of 50%. The procedure was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (IR.MAZUMS..REC.1399.6311). The experiments were conducted consistent with the National Institutes of Health (NIH) guide for the Care and Use of Laboratory Animals.

2.4. Experimental Design

Animals were randomly divided into four groups (six animals in each) as follows: (I) Control, rats fed with standard diet, (II) The hyperthyroidism group, rats with intramuscular injection of levothyroxine, at the dose of 0.3 μg/100g body weight for 2 weeks, (III) rats received methimazole (20 mg/kg body weight), (IV) rats received *D. sophia* extract (900 mg/kg body weight). Group (III) and (IV) were treated by gastric intubation for 2 weeks after levothyroxine injection. The doses of levothyroxine, methimazole, and the extract were selected based on the studies of Josephson et al. [16], Afsharypour et al. [17], and Hosseini et al. [18], respectively.

2.5. Measurement of the thyroid hormones

10% chloral hydrate was used for anesthetizing animals at 0.3 mL/100g. The blood samples were obtained by cardiac puncture and centrifugation (10 min, 4°C). The TSH, FT3, and FT4 levels were processed by the standard method described before [19].

2.6. Histopathological analyses of the thyroid gland

The specimens from the tissue were fixed in formalin solution (10%) for 48 h. Next, it was washed with tap water and dehydrated with ethanol. In order to make the paraffin blocks, the specimens were embedded in paraffin and finally sliced into 5µm sections by a rotary microtome; one section per animal was de-paraffinized and stained using hematoxylin and eosin. Images from the thyroid follicular lumen area were taken using a light microscope (40× magnification) [20].

2.7. Analysis of the data

The Graph Pad Prism Software, version 5.01, was used for analyzing data. The results were analyzed using the one-way analysis of variance (ANOVA) followed by Türkiye's test. The p-value ≤ 0.05 was regarded as significant.

3. Results and Discussion

3.1. The total glucosinolate concentration

The total concentration was measured as 24.14 ± 0.8 mmol equivalent of sinigrin per kilogram of dry seeds via the equation below: $y= 0.361x + 0.1641$, $R^2= 0.9916$.

3.2. Thyroid Hormones

As expected, the TSH levels in the serum decreased in the hyperthyroid group compared to the control ($p<0.0001$), and the FT3 and FT4 levels were elevated significantly in that group. Treatment with *D. sophia* extract significantly increased TSH levels ($p<0.001$) compared to control. Moreover, the FT3 and FT4 levels were also decreased in that group. Methimazole was administered to rats receiving Levothyroxine, and FT3 and FT4 levels were improved. This effect on the levels of the FT3 was more effective than the FT4 (**Figure 1**).

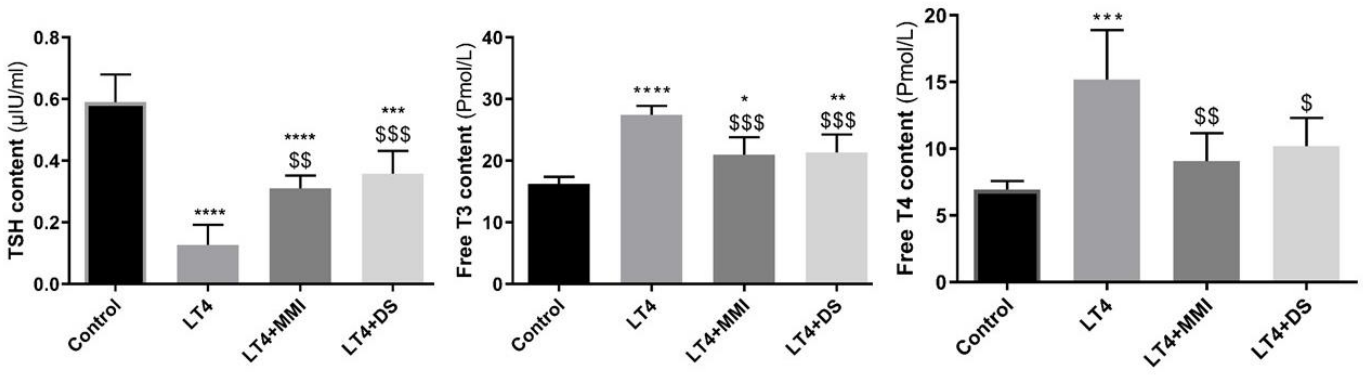

Figure 1. Descurainia sophia seeds extract (DS) affects TSH, FT3, and FT4 levels in hyperthyroid rats. The values were expressed as mean ± SD. (*): significance compared to the control group. ($): significance compared to the levothyroxine group. MMI: group treated with methimazole.

3.3. Histopathology

Based on the photomicrographs (**Figure 2**), the thyroid gland tissue of the control group showed a normal histological appearance, with one layer of follicular cuboidal epithelium. However, in the levothyroxine group, some colloid space was observed in the tissue samples due to the atrophic changes of follicular cells. Moreover, several cytoplasmic vacuoles (shown with a black arrow in **Figure 2B**) appeared in some follicular cells. Moreover, the follicles were mainly lined with flattened thyrocytes, which contained oval nuclei with elevated chromatin density. In some follicles, epithelial cells were removed from the basement membrane and found inside the lumen of the follicle. Blood vessel congestion (shown with the red arrow in **Figure 2B**) and mononuclear cell infiltration (shown with the white arrow in **Figure 2B**) were also abundant in the tissue between the follicles. The histological structure of the rats treated with the extract and methimazole was relatively preserved. Most follicles appeared with cuboidal epithelial cells and homogenous acidophilic colloids. However, few follicles with evacuated or dehydrated colloids were observed. Moreover, the mononuclear cell infiltration was observed. However, it was less than the levothyroxine group.

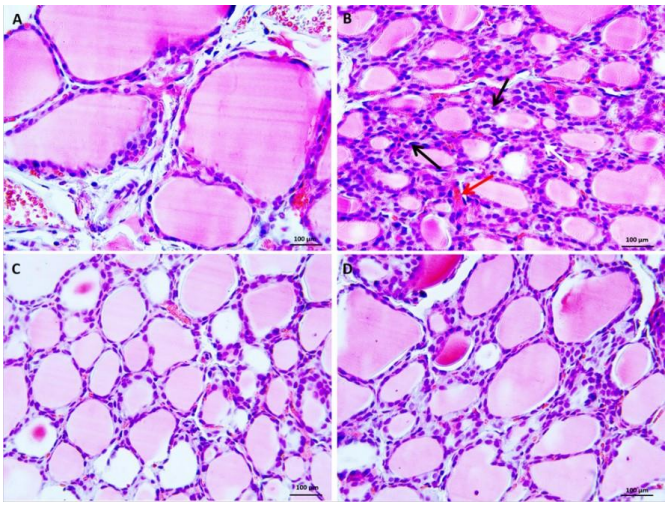

Figure 2. The thyroid follicles of control (A) and the treated groups with levothyroxine (B), methimazole (C) and *D. Sophia* extract (D). The black arrow indicates the infiltration of intense inflammatory cells. The red arrow indicates the blood vessel congestion, and the white arrow indicates the mononuclear cell infiltration. (×40 magnification, hematoxylin and eosin staining, scale bar = 100 mμ).

3.4. Discussion

The present study investigates the protective activities of 70 % hot methanol extract from *Descurainia sophia* seeds on the thyroid damage induced by levothyroxine in rats. The results indicate that the intervention has led to the positive effects, demonstrating its potential benefits in the study context. Compared to the control, the levels of TSH were significantly elevated in the group treated with extract. Further, the treatment group showed a notable reduction in FT3 and FT4 hormone levels. The administration of D. Sophia extract properly improved the histological appearance of the thyroid gland in animals. This improvement was similar to those receiving standard medicine.

Generally, the hyperthyroidism treatment includes symptom relief, along with radioactive iodine therapy, antithyroid pharmacotherapy, and thyroidectomy. These treatment options may cause side effects or damage to the thyroid gland. Therefore, investigating some new therapeutic sources with low adverse effects can be helpful for thyroid dysfunction therapy [21]. The integration of plant-based therapeutic agents into treatment regimens for hyperthyroidism reflects a growing interest in complementary and alternative medicine approaches, highlighting their potential benefits when used alongside conventional therapies [22]. The relation between the intake of some Brassicaceae plants and the development of goiter or hypothyroidism is an important issue that, to date, only a few scientific reports have investigated [23, 24].

Based on recent studies, the seeds of *D. sophia* possess a high amount of some goitrogenic GSLs, including gluconapin (3-butenyl glucosinolate), which enzymatically hydrolysis to goitrin, which exposure to can interfere with the normal function of the thyroid by reducing iodine absorption, the essential element for the synthesis of thyroid hormones [25, 26]. This results in decreasing synthesis of FT3 and FT4 thyroid hormones and excessive secretion of TSH, which causes hypothyroidism [25]. Accordingly, administering *D. Sophia* extract to the hyperthyroid rats in our study altered the hormonal imbalance induced by levothyroxine by elevating the TSH and decreasing the FT3 levels. This compensatory increase in TSH levels is due to the negative feedback between TSH and thyroid

hormones [27]. The results of the present study are in line with the investigation of Paśko et al. [13] which the addition of lyophilized *Brassica napus* (Brassicaceae) to the diet of hyperthyroid rats for 8 weeks improved the adverse effects of sulfadimethoxine (for induction of hyperthyroidism) or iodine deficiency by increasing the TSH levels and reducing the FT3 levels, without any significant effects for FT4 levels. In a previous study by Ikeda et al. [28], the authors conducted a longer experiment (10 weeks), and they did not observe any significant differences in the serum levels of TSH and FT3 hormones. However, the concentrations of FT4 were significantly decreased. More time is needed to achieve effective changes in FT4 levels.

In a similar study that we conducted at the same time on hyperthyroid patients, the two-month consumption of *D. Sophia* capsule resulted in positive changes in clinical and biochemical parameters of thyrotoxicosis in that the insomnia, nervousness, irritability, tremor dyspnea, and heat intolerance were significantly reduced. The hormonal imbalance (TSH, FT3, and FT4) was significantly improved in the patients [29].

In this study, the spectrophotometric analysis of *D. Sophia* seeds extract showed the presence of GSL at the concentration of 24.14 ± 0.8 mmol, equivalent to sinigrin per kilogram in dry seeds.

Based on the latest studies on the GSL analysis of some Brassicaceae plants, the total glocosinolate content of *Lepidium sativum*, *Lepidium perfoliatum*, and *Alyssum linifolium* extract was calculated with the same method as 27.4, 25.0, and 23.28 mmol of sinigrin equivalents per kilogram of dried seeds, respectively [8, 30, 31]. The alleviating effects of *D. Sophia* seeds extract in hyperthyroidism may be related to GSLs such as gluconapin in the plant seeds.

One of the important limitations of the present study is the lack of determination of toxicity patterns of *D. sophia* seeds extract, which should be performed in our future studies.

4. Conclusion

This is the first report about the effectiveness of *D. Sophia* extract on thyroid damage in animal models. Based on the findings, the 70% hot methanol extract from the plant seeds provided extremely protective effects against hyperthyroidism in rats via decreasing serum FT3 and FT4 and increasing TSH levels. These hormonal changes were also supported by histological analysis, which indicated the improved thyroid gland architecture. Detailed investigations are needed to understand the exact mechanism of action of *D. sophia* seed extract on hyperthyroidism.

Ethics

Ethics Committee Approval:
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Athors Contributions

Concept: M.A., Design: M.A., Z.K, F.T. A, M.SH, Data Collection or Processing: F.F., F.M., Analysis or Interpretation: M.A., Z.K, F.T. A, M.SH, Literature Search: F.F., F.M., Writing: F.F., F.M., M.A., Z.K, F.T. A.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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