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Research Paper

# The Effect of an Aqueous Extract of *Illicium Verum* on Serum Levels of Thyroid Hormones and Depression, Anxiety, and Stress in Patients With Hypothyroidism

**Yaghob Koushan[1], Ahmad Yari Khosroushahi[2,3], Mohammad Hossein Geranmayeh[3], Sima Hashemipour[4], Mahnaz Ghadimi Yari[5], Hossein Khadem Haghighian[4*]**

*1. Independent Researcher in Traditional Medicine, Tabriz, Iran.*
*2. Department of Medical Nanotechnology, Faculty of Advanced Medical Science, Tabriz University of Medical Sciences, Tabriz, Iran.*
*3. Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
*4. Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran.*
*5. Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.*

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## ABSTRACT

**Background:** Hypothyroidism has been associated with complications such as increased inflammation, and oxidative stress.

**Objective:** This pilot study was created to assess the impact of *Illicium verum* (*I. verum*) on serum levels of thyroid hormones as well as depression, anxiety, and stress in hypothyroidism patients given the detrimental effects of oxidative stress on thyroid function and considering the antioxidant properties of *I. verum*.

**Methods:** In this double-blind clinical research with a placebo group, which was performed as a pilot, 20 hypothyroid individuals were recruited. Participants were randomly allocated to a capsule containing 1.5 g of *I. verum* (per day) (n=10) or a placebo (n=10) for 8 weeks. Thyroid hormones, including free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were measured at the beginning and end of the study. Furthermore, depression and stress were assessed using the Depression Anxiety Stress Scales-21 (DASS-21) survey. Quantitative analysis was performed using SPSS software, version 20.

**Findings:** No discernible difference was observed between the blood thyroid hormone levels at the baseline. TSH levels in the intervention group decreased significantly at the end of the study, while FT3, FT4, T3, and T4 levels increased significantly ($P<0.05$). Compared to the study's initial findings, the intervention group experienced considerably lower mean changes in terms of depression, anxiety, and stress scores. ($P<0.05$).

**Conclusion:** The *I. verum* supplement can be helpful as a dietary supplement with antioxidant properties in patients with hypothyroidism. This herbal supplement can increase the effectiveness of medication in patients with hypothyroidism.

*** Corresponding Author:**
*Hossein Khadem Haghighian, PhD.*
***Address:*** *Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran.*
***Phone:*** *+98 (914) 8375283*
***E-mail:*** *khademnut@yahoo.com*

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## 1. Introduction

Thyroxine (T4) and triiodothyronine (T3), two hormones, are synthesized by the thyroid gland, one of the largest endocrine glands in the body [1]. Thyroid hormones affect most cell functions in the body and help regulate fat and carbohydrate metabolism. Thyroid hormones are vital in mood, behavior, and health [2]. Hypothyroidism is defined subclinically when thyroid hormones are normal and thyroid stimulating hormone (TSH) is higher than the reference values [3]. Symptoms of hypothyroidism include fatigue, weight gain, dyslipidemia, mental disorders, memory loss, anxiety, depressive symptoms, cardiovascular disorders, and an increased risk of coronary heart disease and death [4]. Hypothyroidism can be divided into three categories, in the first type, the disease is a disorder of the thyroid gland; in the second and third types, it is a secondary disease. The cause of this disorder is the secretion of TSH, which is caused by disorders in the hypophysis and hypothalamus glands, respectively. Successful treatment of this hormonal disease requires that thyroid hormone levels in peripheral tissues return to normal [5]. Levothyroxine is currently used in the treatment of hypothyroidism. Studies have shown that subclinical disorders of thyroid function lead to metabolic diseases, such as cardiovascular disease [6]. However, complications, such as increased inflammation, oxidative stress, and insulin resistance (IR) are associated with hypothyroidism. According to scientific evidence, the hypothalamic-pituitary-thyroid bloc is crucial to maintain the body's free radical balance [3]. The increase in the concentration of TSH in patients with hypothyroidism leads to a decrease in antioxidant defense. It was demonstrated that mice with hypothyroidism had serum levels of the catalase enzyme, total antioxidant capacity (TAC), and lipid peroxidation index which were higher in this group than in the control group [7]. This disorder can be caused by increased oxidative stress and also lead to an increase in this condition. Various studies have shown the effect of receiving antioxidants in reducing the incidence of this disease [8]. Star Anise, also known as *Illicium verum* (*I. versum*), is a fragrant evergreen tree. This plant's low toxicity to humans is one of its key traits. Its primary chemical compounds include volatile compounds, lignans, monoterpenoids, tropenoids, and phenylpropanoids [9]. The anti-inflammatory, painkiller, anticonvulsant, and anesthetic properties of *I. verum* have all been documented in numerous studies. Trans-anethole, one of the most crucial components of plant flavonoids, has been reported to have anti-tumor exercise against fibrosarcoma, cervical cancer, and Ehrlich ascites tumors [10]. Based on the results of scientific studies, the effectiveness of this plant in the treatment of pathophysiological conditions, such as epilepsy, gastrointestinal disorders, diabetes, anxiety, and depression has been determined [11]. Therefore, due to the prevalence of improper eating habits that increase the prevalence of metabolic diseases [12] or considering that no specific treatment and clinical guideline exist to improve the condition of these patients, a study to help treat people with hypothyroidism with an approach of reducing oxidative stress in these people seems essential. Considering the reported antioxidant effects of *I. verum* and the lack of a human study to supplement this plant in this disease, the present study (a pilot study) was designed to investigate the effect of *I. verum* on thyroid hormone status and depression, anxiety, and stress in people with hypothyroidism.

## 2. Materials and Methods

### Patients

The subjects in this study were patients referred to the endocrinology and metabolism clinic of Qazvin University of Medical Sciences based on the clinical consultant's recommendation. After explaining the generalities of the project, the demographic questionnaire, including the inclusion and exclusion criteria, was completed. The inclusion criteria for volunteers included hypothyroidism, willingness to cooperate, age 24-55 years, no change in treatment or medications for at least the last 2 months, and an average level of physical activity [13]. The exclusion criteria for this study included having diabetes, pregnancy and lactation, body mass index (BMI) >30, patients with severe renal and hepatic disorder, any acute illness that may affect the study (cardiovascular patients, lung patients, kidney patients, cancer patients), changes in diet and physical activity, take any dietary supplement from 2 months before the end of the study, alcohol consumption, occurrence of any side effects and unwillingness to cooperate until the end of the project.

### Study design

This randomized, double-blind, placebo-controlled clinical trial research was conducted to test 1.5 g I. quam extract daily diet for 8 days to determine the impact on serum levels of thyroid hormones in individuals with hypothyroidism. Socioeconomic characteristics, medical history, and current pharmaceuticals of patients were recorded after justification. Height, weight, and BMI were measured. Qualified patients were matched for age, sex, and demographic measurements. Patients were randomly

divided into two groups of intervention (*I. verum* extract) (n=10) and placebo (n=10). Sampling in this study was performed using simple random sampling using random numbers. During the intervention, patients received about 20 mg/kg daily of *I. verum* extract, which for a person weighing 72 kg, took 1.5 g (3 capsules of 500 mg) in three divided doses, after each meal. The control group also received 500- mg capsules containing wheat flour, which looked completely like the supplement. According to the latest scientific references, the time required to change thyroid hormones was six weeks [14], and the duration of our study was 8 weeks. Capsules were prepared by someone else outside the project and placed in groups A and B in the same package so that the investigator and patients were unaware of the contents of the capsules. The depression anxiety stress scales-21 (DASS-21) was used to measure depression, anxiety, and stress. This questionnaire is self-administered and assesses the symptoms of depression, anxiety, and stress in the past week. This questionnaire consists of 21 questions and includes subsets of anxiety, depression, and stress. Each subset has 7 questions, and the final score of each section is obtained through the sum of the scores of the related questions. The validity and reliability of this questionnaire in Iran have been studied [15]. Patients were interviewed using a 3-day dietary recall questionnaire at the beginning and end of the research, and subjects with average levels of physical activity were enrolled to account for confounding factors of dieting and activity. Three-day food recalls were used to assess dietary intake, and the nutritionist IV program modified for Iranian food composition was used to estimate the dietary intake of participants. We also used the International Physical Activity Questionnaire (IPAQ) to assess physical activity. Using established guidelines, International Physical Activity Questionnaire (IPAQ) data were converted to physiological equivalents (minutes per month) [13]. Phone monitoring was used to monitor patients' capsule consumption and stop them from falling out once every seven days. Therefore, individuals who consumed fewer than 10% of the capsules were excluded from the study. Each participant was required to return the bottle containing their product.

### Extract preparation

The aqueous extract of *I. verum* powder was separated by distilled water by the standard method, and after mixing, the extracts were dried and ground, and prepared by mixing with the vegetable substrate to yield 500 mg tablets. To prepare an aqueous extract of *I. verum* for each patient, 900 g of its powder was distilled in 3000 mL of water. After heating for 20 minutes, the mixture was passed through a strainer and centrifuged at 3000 rpm for 20 minutes. In the next step, the supernatant was separated and dried. (Dry powder consisted of all parts of the plant.) About 90 g of the extract was obtained from this amount of powder. For two months of consumption, 1.5 grams of the extract was prescribed daily.

### Laboratory methods

After 12 hours of fasting, ten cc of venous blood was taken from the participants. Centrifugation was used to separate the serum, which was then frozen at a temperature of 20° C. Samples were then kept at an 80°Cfor later laboratory testing. Thyroid hormones, including free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), and total thyroxine (TT4) using radioimmunoassay (RIA) and TSH by IRMA (Immunoradiometric assay) using an Immunotech kit made in the Czech Republic were measured. The normal range for TSH was from 0.3 to 3.4, for T4 from 9.5 to 25, and for TT3 from 3.5 to 7.5. Intra-assay and inter-assay coefficients of variation for FT3 were 6.4% and 5.5%, for FT4, 8.3% and 7.5%, for TT3, 5.4% and 5.9%, for total thyroxine (TT4), 5.1% and 6.4%, and for TSH, it was 3.1% and 5.7%, respectively.

### Sample size

This study was conducted as a pilot, and 10 patients were considered in each group (intervention group and placebo group).

### Statistical analyses

SPSS software, version 20 was used for the statistical analysis. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Data were expressed as mean and frequency for quantitative and qualitative variables, respectively. A paired t-test was used to compare the means of quantitative variables in each group, and an independent t-test was used to compare the means between the two groups. Differences were considered statistically significant at $P<0.05$.

## 3. Results

In this study, of the 37 volunteers, 14 patients did not enter the study due to a lack of inclusion criteria, three people did not enter the study due to not signing the informed consent, and finally, 20 people started the study with informed consent. At the end of the study, one patient, for personal reasons, did not complete the study (Figure 1).

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**Table 1.** The comparison of baseline characteristics of the participants

| Variables | | Mean±SD | | P1 |
|---|---|---|---|---|
| | | Placebo (n= 9) | *Illicium verum* (n=10) | |
| Age (y) | | 38.11±3.29 | 37.44±4.36 | 0.411 |
| Height (cm) | | 162.59±9.27 | 164.91±10.06 | 0.744 |
| Weight (kg) | Before | 69.17±7.15 | 68.95±8.5 | 0.621 |
| | After | 69.00±7.09 | 68.00±7.81 | 0.533 |
| | P2 | 0.709 | 0.611 | - |
| Body mass index (kg/m²) | Before | 26.16±0.83 | 25.35±0.08 | 0.239 |
| | After | 26.1±0.08 | 25.00±0.071 | 0.198 |
| | P2 | 0.411 | 0.385 | - |
| Physical activity | Before | 35.11±3.19 | 36.04±2.87 | 0.406 |
| | After | 35.66±3.74 | 36.73±3.26 | 0.39 |
| | P2 | 0.523 | 0.616 | - |

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P1: Comparison of the mean baseline characteristics between the two groups of *Illicium verum* and placebo (independent samples t-test)

P2: Comparison of the mean of baseline characteristics in each group at baseline and the end of the study (paired samples t-test).

As a result, 19 people completed the study, and 95% of them did so according to drop-out. This medical study lasted for eight days. Table 1 lists the patient demographics and baseline characteristics. The primary traits of the patients in the study did not differ significantly between the two groups, according to the information in this table. In terms of anthropometric factors at the beginning and end of the study, no appreciable difference was observed between the two groups (P>0.05).

Table 2 presents the usual daily intake of energy, macronutrients, and nutrients. According to these findings, no discernible difference was observed between the monthly average intakes of energy, protein, fat, or some micronutrients (P>0.05).

Table 3 presents how the aqueous extract of *I. verum* affects the serum levels of thyroid hormone in patients. As can be seen in Table 3, at the beginning of the study, no discernible difference was observed between thyroid hormone serum levels. At the end of the study, TSH levels of the intervention group significantly decreased, while their FT3, T4, T3, and T4 levels increased. This increase was significant (P=0.05). The mean changes in the placebo group between the beginning and end of the study were not significant (P>0.05) (Table 3).

Table 4 presents a summary of the scores for depression, anxiety, and stress conditions. According to the data collected at its conclusion, the mean changes in the intervention group in depressive, anxious, and stress scores were significantly lower than at the start of the study, (P<0.05). At the end of the study, the placebo group did not experience these changes (P>0.05).

### Safety and adverse events

In the study, no side effects were reported. Additionally, this study did not include any co-interventions.

## 4. Discussion

In patients with hypothyroidism, this study was conducted to investigate how *I. verum* affects thyroid hormone levels as well as depression, anxiety, and stress conditions. According to the study's findings, consuming 1.5 g of this plant for 8 weeks significantly decreased TSH levels while raising FT3, T4, T3, and T4 levels. According to database searches, this supplement has

**Table 2.** The comparison of the dietary intake at baseline and the end of the study in hypothyroid patients

| Variables | | Mean±SD | | P1 |
|---|---|---|---|---|
| | | Placebo (n=9) | *Illicium verum* (n=10) | |
| Energy (kcal) | Baseline | 2408.45±265.09 | 2481.08±303.25 | 0.65 |
| | End | 2400.0± 250.058 | 2435.84±289.11 | 0.78 |
| | P2 | 0.809 | 0.711 | - |
| Protein (gr) | Baseline | 80.07±14.2 | 81.22±19.04 | 0.401 |
| | End | 79.86±22.11 | 81.09±27.31 | 0.238 |
| | P2 | 0.356 | 0.569 | - |
| Carbohydrate (gr) | Baseline | 300.47±58.04 | 319.18±39.05 | 0.44 |
| | End | 299.29±39.44 | 316.28±45.44 | 0.508 |
| | P2 | 0.699 | 0.59 | - |
| Fat (gr) | Baseline | 97.5±16.22 | 97.3±15.07 | 0.419 |
| | End | 95.18±24.18 | 96.17±15.07 | 0.488 |
| | P2 | 0.309 | 0.41 | - |
| Saturated fatty acids (gr) | Baseline | 32.05±7.19 | 31.85±6.39 | 0.219 |
| | End | 31.24±5.34 | 31.11±6.44 | 0.394 |
| | P2 | 0.207 | 0.35 | - |
| Monounsaturated fatty acid (gr) | Baseline | 34.13±5.77 | 32.14±6.22 | 0.313 |
| | End | 32.07±4.28 | 31.17±5.66 | 0.396 |
| | P2 | 0.274 | 0.402 | - |
| Polyunsaturated Fatty acid (gr) | Baseline | 30.46±5.93 | 31.27±7.11 | 0.257 |
| | End | 29.65±6.08 | 31.07±7.03 | 0.143 |
| | P2 | 0.199 | 0.29 | - |
| Fiber (gr) | Baseline | 14.29±2.53 | 15.69±2.58 | 0.28 |
| | End | 14.01±3.19 | 14.88±3.12 | 0.294 |
| | P2 | 0.49 | 0.215 | - |
| Vitamin C (mg) | Baseline | 73.25±19.23 | 74.18±12.44 | 0.506 |
| | End | 72.5±20.33 | 74.00±24.03 | 0.397 |
| | P2 | 0.466 | 0.701 | - |
| Vitamin E (IU) | Baseline | 13.59±2.33 | 14.77±3.04 | 0.096 |
| | End | 12.46±2.28 | 13.99±2.22 | 0.871 |
| | P2 | 0.183 | 0.104 | - |
| Selenium (µg) | Baseline | 116.28±37.14 | 119.27±44.1 | 0.425 |
| | End | 115.95±37.6 | 119.33±61.07 | 0.303 |
| | P2 | 0.661 | 0.746 | - |

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P1: Comparison of the mean of dietary intakes between the two groups of *Illicium verum* and placebo (independent samples t-test)

P2: Comparison of the mean of dietary intakes in each group at baseline and the end of the study (paired samples t-test)

**Table 3.** Changes in baseline to endpoint measures for thyroid hormones in two groups

| Variables | | Mean±SD | | P1 |
|---|---|---|---|---|
| | | Placebo (n=9) | *Illicium verum* (n=10) | |
| FT3 (pmol/l) | Baseline | 4.61±0.85 | 4.69±0.64 | 0.391 |
| | End | 4.73±0.34 | 6.14±0.43 | 0.02 |
| | P2 | 0.362 | 0.02 | - |
| FT4 (pmol/L) | Baseline | 17.27±4.75 | 17.58±4.22 | 0.44 |
| | End | 17.52±4.46 | 21.96±5.13 | 0.01 |
| | P2 | 0.591 | 0.01 | - |
| TT3 (ng/mL) | Baseline | 1.69±0.56 | 1.73±0.29 | 0.167 |
| | End | 1.74±0.39 | 2.12±0.41 | 0.03 |
| | P2 | 0.159 | 0.03 | - |
| TT4 (µg/dL) | Baseline | 8.15±0.37 | 8.29±0.63 | 0.601 |
| | End | 8.23±0.81 | 9.89±0.75 | 0.02 |
| | P2 | 0.53 | 0.02 | - |
| TSH (mIU/L) | Baseline | 3.69±0.66 | 3.8±0.41 | 0.109 |
| | End | 3.55±0.29 | 2.0±0.34 | 0.04 |
| | P2 | 0.267 | 0.033 | - |

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P1: Comparison of the mean of the thyroid hormones between the two groups of *Illicium verum* and placebo (independent samples t-test)

P2: Comparison of the mean of the thyroid hormones in each group at baseline and the end of the study (paired samples t-test)

Abbreviations: FT3: free triiodothyronine; FT4: free thyroxine; TT3: total triiodothyronine; TT4: total thyroxine; TSH: thyroid stimulating hormone

not been used in a clinical study on thyroid patients. Antibodies attacking the thyroid gland are the main cause of hypothyroidism, which results in inadequate thyroid hormone production of T3 and T4 and sluggish metabolism [16]. The serum level of thyroid hormones must be at normal levels to treat hypothyroidism because the thyroid plays a crucial and effective role in the body's metabolic processes [2].

Although various factors contribute to the onset and progression of hypothyroidism, recent research has focused particularly on the part that oxidative stress plays in the disease's pathogenesis [17]. An imbalance between the production of free radicals and reactive oxygen species (ROS) and the antioxidant defense system results in oxidative stress. In aerobic biological systems, antioxidant defense mechanisms neutralize or minimize these invasive agents to counteract free radicals [18]. The body produces some of these immune system components, such as the enzymes catalase, superoxide dismutase, and glutathione peroxidase, but the diet may provide other nutrients, such as vitamin E and vitamin C [19]. Medical studies have shown that hypothyroidism patients have significantly lower catalase activity levels than healthy people [20]. However, because antioxidant depletion can result in non-chronic metabolic diseases, medical researchers are currently paying close attention to assessing the total antioxidant capacity. Cancer, diabetes, and hypothyroidism are just a few diseases that are associated with decreased total antioxidant capacity [18]. In astudy conducted by Akinci et al., the status and performance of antioxidant system in people with thyroid cancer were assessed. According to the study's find-

**Table 4.** Changes in baseline to endpoint measures for depression, anxiety, and stress scores in two groups

| Variables | | Mean±SD | | P1 |
|---|---|---|---|---|
| | | Placebo (n=9) | *Illicium verum* (n=10) | |
| Depression | Baseline | 11.19±3.09 | 12.01±4.13 | 0.411 |
| | End | 11.00±3.21 | 9.12±3.17 | 0.04 |
| | P2 | 0.548 | 0.032 | - |
| Anxiety | Baseline | 11.85±3.36 | 12.1±3.67 | 0.449 |
| | End | 11.67±3.08 | 7.81±2.19 | 0.029 |
| | P2 | 0.56 | 0.022 | - |
| Stress | Baseline | 18.64±4.41 | 18.93±4.18 | 0.657 |
| | End | 18.09±4.12 | 12.25±3.55 | 0.02 |
| | P2 | 0.595 | 0.011 | - |

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P1: Comparison of the mean of the depression, anxiety, and stress scores between the two groups of *Illicium verum* and placebo (independent samples t-test)

P2: Comparison of the mean of the depression, anxiety, and stress scores in each group at baseline and the end of the study (paired samples t-test)

ings, thyroid cancer is associated with an imbalance in the oxidant/antioxidase system [21]. Also, scientific research has shown that many plants contain certain compounds that affect the level of thyroid hormone [22]. Flavonoids are one of the crucial phenolic groups that have antioxidant properties and are abundantly found in fruits, vegetables, seeds, roots, and stems. The mechanism of action of plant flavonoids is through the inhibition of thyroid peroxidase [23]. The main chemical compounds of *I. verum* include monoterpenoids, terpenoids, phenylpropanoids, lignans, flavonoids, and active compounds. This plant has antimicrobial, antiviral, antioxidant, anti-inflammatory, analgesic, and estrogenic properties [10]. Plants or foods with antioxidant properties can help treat hypothyroidism by neutralizing free radicals and reducing inflammation. However, no clinical trials have been published in scientific databases on the supplementation of this plant in patients with hypothyroidism. However, the findings of other animal experiments show the anti-inflammatory and antioxidant properties of *I. verum*. In a study conducted by Farahmand et al., which examined the effect of *I. verum* supplementation on the severity of symptoms in people with premenstrual syndrome (PMS), the results showed that *I. verum* was effective in decreasing the symptoms compared to A placebo [24]. Also in the study of Asif et al., it was shown that *I. verum* has anti-cancer properties and prevents colon cancer due to its antioxidant effects [25]. According to both animal and human studies, thyroid disorders increase peroxidation reactions and ROS production. Lipid peroxidation is a mechanism that leads to oxidative damage to cell membranes [18]. The effects of *I. verum* in improving thyroid function in people with hypothyroidism may be related to the antioxidant properties of micronutrients in this plant, which increase thyroid hormones by reducing lipid peroxidation and improving oxidative stress in favor of antioxidants. In the study of Chakrabarti et al., it was found that the L- thyroxine drug, in addition to increasing the FT4 and reducing the TSH in people with hypothyroidism, reduced malondialdehyde (MDA) levels in the drug group. This factor is one of the most basic and well-known indicators for measuring lipid peroxidation [26].

In addition to biochemical factors, *I. verum* intake reduced the score related to depression, anxiety, and stress compared to the placebo group. According to the findings of Fathizadeh et al., aerobic exercise for eight weeks effectively improved depression, anxiety, and stress in women with hypothyroidism [27]. In some clinical studies, patients with major depressive disorder have been reported to have oxidative disorders, including oxidative damage to erythrocyte membranes, manifested by a decrease in omega-3 fatty acids. This also includes high

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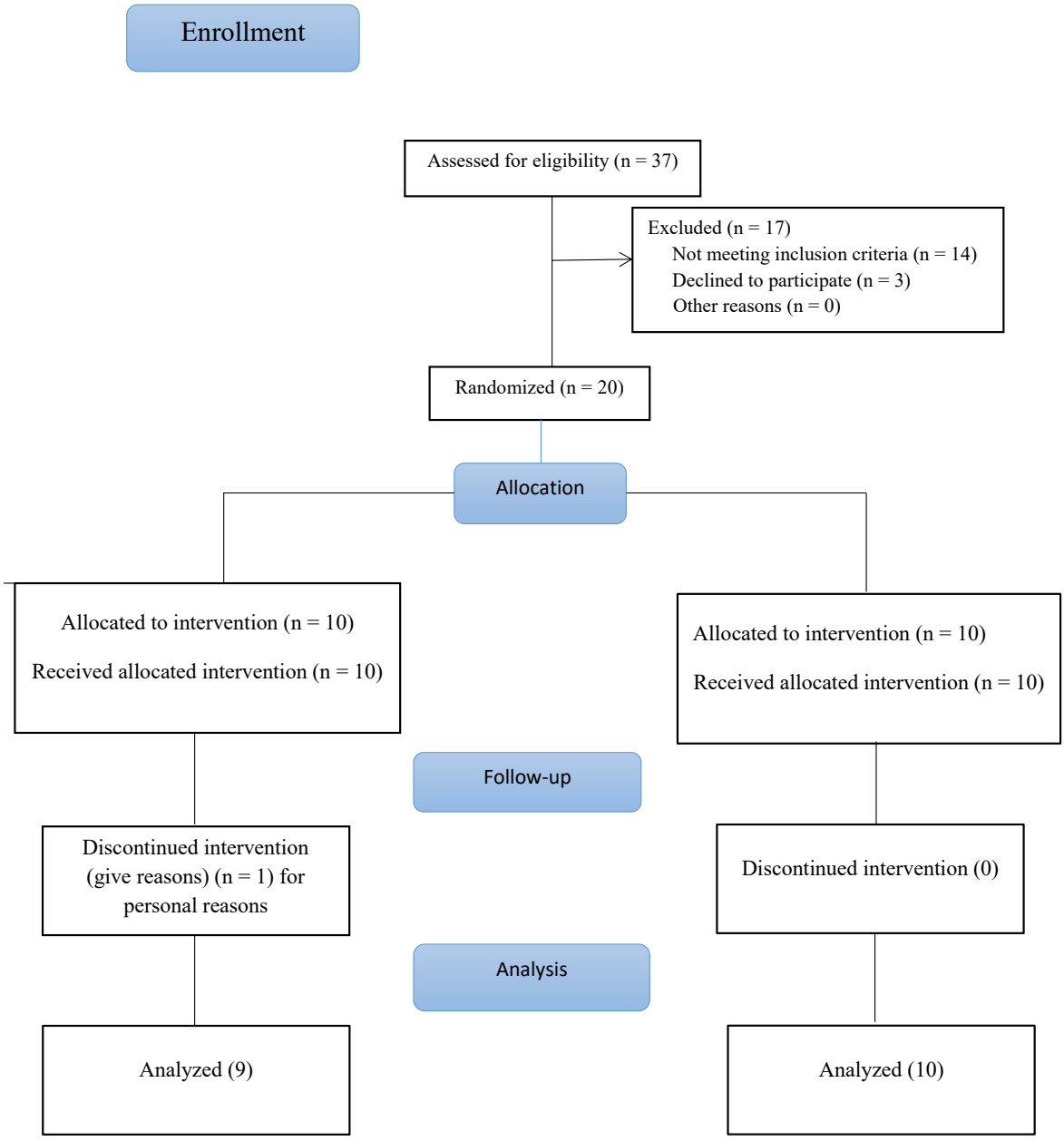


**Figure 1.** Trial profile and design

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levels of lipid peroxidation; oxidative damage to genetic material, and decreased concentrations of endothelial nitric oxide synthase (NOs) inhibitors. It has been reported that increased production of ROS may disrupt membrane phospholipids and ultimately affect nerve membranes, resulting in changes in membrane viscosity that may affect the function of serotonergic and catecholaminergic receptors [28]. In people with hypothyroidism, increased oxidative stress exacerbates depression and anxiety [21]. The psychological impact of this disease may be reduced by prescribing antioxidants and enhancing the body's antioxidant system. As with other studies, this clinical pilot study may have advantages and disadvantages. The fact that *I. verum* extract supplementation on serum thyroid hormone levels in hypothyroidism was examined for the first time is one of the study's strengths. The results of this study were significant because it was designed as a double-blind, randomized clinical trial. However, the results of this study have been statistically analyzed due to the low budget, the small number of participants, and the intervention's length. However, it should be noted that studies with more participants and a longer intervention period are required to draw clinical conclusions and examine the clinical effects.

## 5. Conclusion

According to the study's findings, people with lower TSH levels experienced lower TSH levels after taking *I. verum* supplements for 8 weeks at 1.5 g per day, while their FT3, T4, T3, and T4 levels increased. These findings lend credence to the idea that the polyphenol antioxidant class can significantly influence hypothyroidism by lessening its negative effects.

## Ethical Considerations

### Compliance with ethical guidelines

The study was approved by the Ethical Committee of Qazvin University of Medical Sciences with a number of IR.QUMS.REC.1399.521 and also registered with the identification code IRCT20141025019669N18 in the clinical trial registry of Iran. This study was conducted at the Endocrinology and Metabolism Clinic of Qazvin University of Medical Sciences, Qazvin, Iran. Informed consent was obtained from these individuals to participate in the study.

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### Authors' contributions

Conceptualization and interpreting the results: Yaghob Koushan, Ahmad Yari Khosroushahi, and Mohammad Hossein Geranmayeh; Investigation, writing – original draft, and writing – review & editing: Yaghob Koushan and Sima Hashemipour; Supervision and data analysis: Hossein Khadem Haghighian, and Sima Hashemipour; Data collection: Yaghob Koushan, Ahmad Yari Khosroushahi, Mohammad Hossein Geranmayeh and Sima Hashemipour; Funding acquisition and resources: Hossein Khadem Haghighian. All authors revised the manuscript critically and all authors have approved the final version of the article, including the authorship list.

### Conflict of interest

The authors declared no conflict of interest.

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