The Impact of Zingiber Officinale Decoction on Thyroid Functions in Hypothyroid-Induced Rats.

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Abstract— **Background and objective: Zingiber officinale (Ginger) has several pharmacological actions and is extensively employed in traditional medicine for the management of different conditions. This study was designed to evaluate and compare the effects of Ginger with levothyroxine on thyroid function tests and female sex hormone tests in normal and hypothyroid rats.**

Methods: Forty-two female rats were divided into two groups. The initial group consisted of 12 rats, which were then divided into two smaller groups, each containing 6 rats. The first smaller group acted as a control, while the second subgroup was given a Ginger decoction.

The second group consisted of 30 rats with induced hypothyroidism, which were further divided into five smaller groups, each containing 6 rats. The first subgroup served as a positive control group. The second subgroup received aqueous of Ginger. The third subgroup received the decoction with propylthiouracil. The fourth subgroup received levothyroxine. The fifth subgroup received levothyroxine with propylthiouracil.

Results: Ginger administration significantly increased serum T3 and decreased serum T4 levels in normal rats. Notably, both ginger and levothyroxine significantly increased serum T3 and T4 levels in hypothyroid rats. In normal rats, daily ginger administration significantly increased serum estrogen and decreased serum progesterone levels. However, in hypothyroid rats, it did not significantly affect either estrogen or progesterone levels.

Key: Ginger, Thyroid function, Hypothyroid female rats

I.INTRODUCTION

Hypothyroidism is the most common endocrine disorder arising from thyroid hormone insufficiency, it can be classified into primary, and secondary. Primary hypothyroidism is due to gland destruction and secondary hypothyroidism is due to the failure of adequate thyroid-stimulating hormone (TSH) secretion and release from the pituitary gland or thyrotrophin-releasing hormone (TRH) from the hypothalamus [1].

Several herbal remedies have shown promise in managing hypothyroidism. For example, Bauhinia purpurea extract increased both T4 and T3 levels in female mice, while Withania somnifera raised serum T4 but not T3 levels [2]. Studies have also demonstrated that different doses of Elettaria Cardamomum hydroethanolic extract significantly increased T3 and T4 serum levels in male mice [3]. Additionally, Costus pictus extract restored thyroid hormone levels in experimental hypothyroidism of rats [4].

Ginger (Zingiber officinale) holds significant importance in traditional medicine, where it has been used for thousands of years in China, India, and other countries to treat various diseases, including symptoms of hypothyroidism such as weight gain [5]. It possesses a wide range of pharmacological activities, including anticancer and antioxidant properties [6]. The powdered rhizome of ginger contains fatty oil, protein, carbohydrates, crude fiber, and volatile oil [7]. Its primary essential volatile oils are monoterpenoid compounds [8]. Ginger also boasts strong antioxidant properties due to its polyphenolic compounds, vitamins, and minerals [9, 10].

Despite the promising applications of various herbal remedies in managing hypothyroidism, the impact of ginger extract on thyroid hormones remains unexplored. Therefore, this study aimed to evaluate the potential effects of aqueous ginger extract on thyroid function and female sex hormone levels in both normal and hypothyroid rats.

II.MATERIALS AND METHODS

2.1 Plant Material

Zingiber officinale Roscoe (ginger) rhizomes were obtained from a private local herbal market. The ginger was prepared using the decoction method. Whole rhizomes were cleaned, dried, and finely powdered. To prepare an aqueous decoction, 100 grams of powdered ginger rhizome were added to a flask containing 1000 mL of distilled water. The mixture was boiled for 15 minutes. The resulting extraction solution was filtered through a funnel containing cotton wool to remove coarse particles. The filtrate was then passed through filter paper to eliminate any remaining fine particles of the powdered rhizome. Finally, the filtrate was diluted with water to achieve the desired volume.

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2.2 Animals

Forty-two adult female rats weighing between (100-250 g) were used in this study. All animals kept in the animal house, under the controlled condition of 12 hours' light and 12 hours' dark cycle in a room temperature of 27 Centigrade. The experiments were carried out with the approval of the ethic committee of Hawler Medical University/College of Medicine

2.3 Experimental Design

Forty-two rats were divided into two groups. The first group, consisting of 12 rats, received a regular diet throughout the study. This group was further divided into two subgroups of 6 rats each: a control group receiving no treatment and an experimental group receiving a 10% (w/v) ginger rhizome solution at a dose of 400 mg/kg for four weeks.

The second group comprised 30 rats with induced hypothyroidism. Hypothyroidism was induced by adding propylthiouracil (0.1% w/v) to their drinking water at a dose of 4 mg/kg for four weeks.

This group was then subdivided into five subgroups of 6 rats each:

Subgroup 1: Positive control (hypothyroid rats receiving no treatment)

Subgroup 2: Received a 10% (w/v) aqueous ginger rhizome decoction orally at 400 mg/kg daily for four weeks.

The third subgroup received an aqueous ginger rhizome decoction (10% w/v) orally at a dose of 400 mg/kg daily for 8 weeks, while concurrently receiving propylthiouracil (4 mg/kg) in their drinking water [11]. The fourth subgroup received a daily oral dose of levothyroxine (20 µg/kg) for four weeks. The fifth subgroup received a daily oral dose of levothyroxine (20 µg/kg) along with propylthiouracil (4 mg/kg) in their drinking water for 8 weeks.

Following the treatment duration, the animals underwent blood biochemical analyses. After an overnight fasting period, blood samples were obtained the following day via cardiac puncture after the rats were anesthetized. The obtained blood was then transferred into designated tubes labeled with numerical identifiers.

These experiments were conducted with the approval of the ethics committee at Hawler Medical University/College of Medicine.

2.4 Statistical Analysis

The data are presented as mean ± standard error. Statistical analysis was performed with SPSS Version 26 software. One-way ANOVA was used for data analysis, followed by unpaired Student's t-test and Duncan test for group comparisons. A p-value ≤ 0.05 was considered statistically significant.

III.RESULTS

3.1 Effects of Zingiber Officinale Roscoe Rhizome on Serum (T3, T4, And TSH) Levels of Normal Rats

Oral administration of a 10% w/v ginger decoction for 28 days significantly increased serum T3 (P=0.044) and decreased serum T4 levels (P=0.005) in normal rats (Table 1).

TABLE 1. EFFECTS OF ZINGIBER OFFICINALE ROSCOE RHIZOME (10%W/V) ON SERUM (T3, T4 AND TSH) LEVELS OF NORMAL RATS (N=6).

Parameters	(Negative Control)	Treated with ZO	P. value
T3 (nmol/L)	0.926±0.494	1.213±0.114	0.044
T4 (nmol/L)	63.295±6.630	38.181±2.134	0.005
TSH (IU/ml)	0.044±0.00183	0.038±0.00174	0.061

ZO, Zingiber officinale; T3, triiodothyronine; T4, tetraiodothyronine; TSH, thyroid-stimulating hormone

3.2 Effects of Zingiber Officinale Roscoe Rhizome And Levothyroxine on Serum (T3, T4, And TSH) Levels of Hypothyroid Rats.

Oral ingestion of propylthiouracil (0.1%) at a dose rate of 4mg/kg in drinking water for 4 weeks, significantly reduced serum (T3 and T4) and non-significantly increased serum (TSH) levels of hypothyroid rats when compared with negative control (Table 2)

There was a statistically significant elevation in serum levels of (T3 and T4) of hypothyroid rats treated by Ginger rhizome (10% w/v) at a dose rate of 400 mg/kg for 4 weeks. Whereas serum level of (TSH) was reduced not significantly by Ginger when compared with the positive control (hypothyroid rats). (Table 2).

Daily oral administration of Ginger rhizome (10% w/v) at a dose rate of 400 mg/kg with receiving propylthiouracil (0.1%) at a dose rate of (4mg/kg) for 8 weeks non-significantly reduced serum level of (T3) and increased serum level of (T4) in hypothyroid rats. While serum level of (TSH) significantly increased when compared with hypothyroid group rats (Table 2).

Oral intake of Levothyroxine at a dose rate of (20 µg/kg) for 4 weeks induced a significant elevation in serum levels of (T3 and T4) of hypothyroid rats, whereas serum level of (TSH) was reduced not significantly when compared with a hypothyroid group (positive control) (Table 3.2.).

Hypothyroid rats treated with Levothyroxine at a dose rate of (20 µg/kg) with receiving propylthiouracil (0.1%) at a dose rate of (4mg/kg) for 8 weeks, significantly increased serum levels of (T3 and T4) of rats, whereas serum level of (TSH) was increased not significantly when compared with hypothyroid rats (positive control) as shown in Table 3.2.

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TABLE 2. EFFECTS OF ZINGIBER OFFICINALE ROSCOE RHIZOME AND LEVOTHYROXINE ON SERUM LEVELS OF (T3, T4, AND TSH) OF HYPOTHYROID RATS (N=30).

Parameters	Study groups					
	Negative Control	HT (Positive control)	HT-ZO	HT-ZO-PTU	HT-T4	HT-T4.PTU
T3 (nmol/L)	0.92 ± 0.05 a	0.32 ± 0.02 b	1.21 ± 0.07 d	0.19 ± 0.01 b	0.86 ± 0.04 a	0.54 ± 0.04 c
T4 (nmol/L)	63.3 ± 6.63 a	14.34 ± 0.45 b	46.02 ± 5.93 a	19.26 ± 1.54 b	230.46 ± 9.3 c	249.4 ± 17.4 c
TSH (IU/ml)	0.029±0.002 ab	0.033±0.004 a	0.032 ±0.0009 a	0.047±0.0015 b	0.029±0.001 a	0.039±0.002 ab

The different letters mean there is a significant difference at $P < 0.05$ Control (CTL), Control (CTL), Hypothyroid (HT), Hypothyroid treated by Zingiber officinale (HT- ZO),
Hypothyroid treated by Zingiber Officinale with receiving propylthiouracil (HT- ZO-PTU),
Hypothyroid treated by Levothyroxine (HT-T4),
Hypothyroid treated by Levothyroxine with receiving propylthiouracil (HT-T4-PTU).

3.3 Effects of Zingiber Officinale Roscoe Rhizome on Serum Levels of Estrogen and Progesterone of Normal Rats

Daily ingestion of 10% w/v ginger rhizome powder at 400 mg/kg significantly increased serum estrogen levels in normal rats ($p = 0.049$).
Conversely, serum progesterone levels in normal rats treated with 10% w/v ginger rhizome powder at 400 mg/kg showed a statistically significant decline ($p = 0.018$) Table 3.

TABLE 3. EFFECTS OF ZINGIBER OFFICINALE ROSCOE RHIZOME (10 % W/V) ON SERUM PROGESTERONE AND ESTROGEN LEVELS OF NORMAL RATS (N=6).

Parameters	Before treatment(Negative control)	Treat with ZO	P. value
Estrogen (pg/ml)	19.581 ±6.979	37.573 ± 5.217	0.0 49
Progesterone (ng/ml)	31.046 ± 6.748	10.710 ± 2.495	0.018

3.4 Effects of Zingiber officinale Roscoe rhizome and Levothyroxine on Serum Levels of Estrogen and Progesterone of Hypothyroid Rats

Daily administration of propylthiouracil (0.1%) at a dose rate of 4mg/kg for four weeks, had led to significant elevation in serum estrogen level and nonsignificant elevation in serum progesterone level of the hypothyroid group (positive control) when compared with negative control (Table 4). Daily administration of Ginger (10% w/v) at a dose rate of 400mg/kg, for four weeks, non significantly decrease both serum levels of estrogen and progesterone of hypothyroid rats when compared with a hypothyroid group (positive control) as shown in Table 3.4.
Hypothyroid rats treated with Ginger (10% w/v) at a dose rate of 400mg/kg with receiving propylthiouracil (0.1%) for 8 weeks, did not significantly increase serum estrogen levels and decreased serum progesterone levels when compared with the hypothyroid group (positive control) (Table.4).
Daily oral receiving of hypothyroid rats by Levothyroxine at a dose rate of (20 µg/kg) for four weeks not significantly reduce serum estrogen and progesterone levels when compared with the hypothyroid group (positive control) (Table 4).
Serum estrogen level was not significantly increased of hypothyroid rats by daily administration of Levothyroxine at a dose rate of 20 µg/kg, with receiving propylthiouracil (0.1%) at dose rate of (4mg/kg) for 8 weeks. Whereas serum progesterone level significantly decreased when compared with the hypothyroid group (positive control) (Table 4)

TABLE 4. EFFECTS OF ZINGIBER OFFICINALE ROSCOE RHIZOME AND LEVOTHYROXINE ON SERUM (ESTROGEN AND PROGESTERONE) LEVELS OF HYPOTHYROID RATS (N=30).

Parameters	Study groups					
	Negative Control	HT (Positive control)	HT-ZO	HT-ZO-PTU	HT-T4	HT-T4-PTU
Estrogen (pg/ml)	19.58 ±6.97 a	60.38 ± 9.6 bc	43.0 ± 3.6 b	60.92 ± 6.2 bc	45.4 ± 2.5 b	69.23 ± 4.9 c
Progesteron (ng/ml)	31.04 ±6.74 ab	36.88 ± 12.9 b	31.60 ± 9.9 ab	18.41 ± 6.9 ab	29.97±10.4 ab	3.52 ± 0.47 a

Control (CTL), Hypothyroid (HT), Hypothyroid treated by Zingiber officinale (HT- ZO),
Hypothyroid treated by Zingiber Officinale with receiving propylthiouracil (HT- ZO-PTU),
Hypothyroid treated by Levothyroxine (HT-T4),
Hypothyroid treated by Levothyroxine with receiving propylthiouracil (HT-T4-PTU).

IV.DISCUSSION

In this study, the decoction of Zingiber officinale (10% w/v) significantly increased serum T3 and significantly decreased serum T4 levels in normal rats. This result could be related to ginger's ability to enhance the conversion of inactive T4 into active T3 due to the presence of nutrient composition such as vitamin C, thiamine (B1), riboflavin (B2), and niacin (B3), along with essential minerals like Zinc, Iron, and Copper [12,13]. Zinc supplementation can reverse hypothyroidism, and Copper is necessary for T4 production. Vitamins act as important antioxidants to neutralize oxidative stress in the thyroid gland [14]. Additionally, Iron, Zinc, and selenium play crucial roles in normal thyroid hormone metabolism and are key to the conversion of T4 into T3. Zinc specifically aids in

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converting inactive thyroid hormone (T4) into its active form (T3). When zinc is deficient, the body tends to produce more reverse T3 [15,16].

A non-significant reduction in serum TSH levels in normal rats due to the effect of ginger rhizome could be related to negative feedback loops within the hypothalamic-pituitary-thyroid (H-P-T) axis, which regulates circulating concentrations of thyroid hormone. The serum levels of thyroid hormones increase (above normal levels) due to the inhibition of the release of thyrotropin-releasing hormone (TRH) and TSH [17].

In the current study, ginger rhizome at a concentration of 10% w/v significantly increased serum T3 and T4 levels in hypothyroid rats. This result suggests that the plant has reversed the actions of propylthiouracil. Propylthiouracil-induced hypothyroidism, through the induction of oxidative stress, inhibits the function of thyroid peroxidase (TPO), which decreases the synthesis of T3 and T4 [18]. Additionally, the non-volatile pungent compounds of ginger, including zingerone, gingerdiol, gingerols, and shogaols, along with some related phenolic ketone derivatives (terpenes), have antioxidant activity [19].

Another reason for the significant elevation in serum T3 and T4 levels in hypothyroid rats due to the effect of ginger could be related to the presence of volatile organic compounds in ginger, such as sesquiterpene hydrocarbons and sesquiterpene [20]. These compounds might affect the sodium iodide symporter, a protein crucial for thyroid hormone production, leading to increased iodine uptake by the thyroid glan [21].

The serum TSH level of rats with hypothyroidism was not significantly reduced after receiving ginger rhizome. This result could be related to the short-term treatment with the plant, which may require more time to reduce TSH levels.

Hypothyroid rats received ginger rhizome at a concentration of 10% w/v continuously with propylthiouracil (0.1% w/v), which led to a non-significant decrease in serum T3 levels and an increase in serum T4 levels. This result suggests that propylthiouracil was more effective than ginger when given together. Since this group received propylthiouracil continuously for 8 weeks, it not only prevents intrathyroidal conversion of T4 into T3 but also suppresses the extrathyroidal conversion of T4 into T3 by blocking deiodinase enzyme function, resulting in diminished T3 active metabolite and elevated T4 prohormone levels [22].

Serum TSH levels significantly increased in the presence of both ginger and propylthiouracil. This result is related to the predominant effect of propylthiouracil over 8 weeks compared to that of the plant. This finding is also in accordance with [23], which concluded that reduced thyroid hormone concentrations activate feedback mechanisms, consequently increasing serum TSH concentration.

Serum T3 and T4 levels significantly increased in hypothyroid rats after taking levothyroxine at a dosage of 20 µg/kg continuously with propylthiouracil (0.1%). This result is attributed to the predominant effect of levothyroxine over propylthiouracil.

In the current study, administration of ginger rhizome at a concentration of 10% w/v significantly increased serum estrogen levels in normal rats. This result could be attributed to the presence of phytoestrogens in ginger. Reports indicate that ginger extract contains flavonoids [24]. . Flavonoids, specifically isoflavonoids, are one of the four main classes of phytoestrogens [25]. Phytoestrogens exhibit a high degree of chemical similarity to mammalian estradiol, enabling them to bind to alpha and beta estrogen receptors [26,27]. Furthermore, another study suggested that the protodioscin content of ginger extract can increase the level of sex steroid hormones [28].

The serum estrogen level in hypothyroid rats significantly increased after administering propylthiouracil (0.1%) compared to the control group. This finding aligns with another study suggesting that propylthiouracil might decrease the liver's production of sex hormone-binding globulin (SHBG). Consequently, lower SHBG levels lead to higher free sex steroid hormones, resulting in the observed increase in estrogen [29].

Ginger rhizome had a non-significant effect on decreasing serum estrogen levels in hypothyroid rats compared with untreated hypothyroid rats. This result is supported by a study indicating that phytoestrogens promote the synthesis of sex hormone-binding globulin (SHBG). Elevated SHBG levels lead to increased binding and, consequently, decreased free estradiol, diminishing the quantity of estrogen available for interaction with estrogen receptors [30].

Levothyroxine at a dosage of 20 µg/kg non-significantly decreased serum estrogen levels in hypothyroid rats after administration for four weeks compared with untreated hypothyroid rats. This result is in accordance with the study by Ito et al. [31], who suggested that Levothyroxine (T4) increases the production and secretion of sex hormone-binding globulin (SHBG) by Hep G2 cells. This increase in SHBG levels leads to a decrease in free sex steroid hormones, and this response is detectable after a few days of treatment.

In the current study, serum progesterone levels significantly decreased after treatment with ginger rhizome in normal rats. This result could be related to the presence of flavonoids in the plant. Flavonoids inhibit 3beta-hydroxysteroid dehydrogenase and delta5/delta4 isomerase, which are essential for the conversion of pregnenolone into progesterone[32,33].

V.CONCLUSIONS

1- Zingiber officinale extract significantly increased serum T3 levels through the conversion of T4 into T3 in normal rats. It also significantly increased serum estrogen levels in normal rats.

2-Ginger significantly increased serum T3 and T4 levels without a significant effect on serum TSH levels in hypothyroid rats.

VI.RECOMMENDATIONS

Ginger supplements should not be taken in large doses or continuously for extended periods, as it may affect thyroid hormones and estrogen level.

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