# Potential Protective Effect of *Laminaria Japonica* Ethanolic Extract on Carbimazole-Induced Hypothyroidism in Male Albino Rats

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## Abstract

Hypothyroidism arises when the thyroid gland does not create enough thyroid hormone. Untreated, hypothyroidism can eventually cause cardiac issues and high cholesterol, among other health issues. *Laminaria japonica* is one of the most important seaweeds, with various health benefits, especially in cases of hypothyroidism, due to its high level of iodine and phenolic compounds. So, this study aimed to evaluate the potential protective effect of different doses of *Laminaria japonica* ethanolic extract (LJEE) on carbimazole-induced hypothyroidism in male rats. Thirty male albino rats were divided into five groups (6/each); control group (G1), treated group (G2) received 1.35 mg/kg carbimazole orally, groups (3-5) received physiological saline and 100, 200, and 300 mg/kg body weight./day LJEE, respectively. An hour later, carbimazole was given orally at the same dose for 21 day. At the end of the experiment, rats were sacrificed and blood samples and thyroid glands were collected for biochemical and histopathological evaluation. Treatment of rats with carbimazole caused a significant decrease ($p \leq 0.05$) in thyroid hormones, antioxidant enzymes (SOD and CAT) and HDL levels in serum. Moreover, levels of MDA markedly increased in the treated group compared with the control group. The pretreatment of rats with LJEE at different doses not only improved thyroid hormones, antioxidants, liver enzymes (AST, ALT, ALP) and TSH levels in serum but also remarkably decreased levels of cytokines (TNF-α, I-6), lipid profiles (TC, TG, LDL, and, VLDL), and serum glucose, and improved both molecular and histological parameters of the thyroid gland. Therefore, LJEE is considered an effective treatment in treating hypothyroidism.

***Keywords.*** Thyroid hormone, Iodine Defficiency, Seaweeds, Antioxidants, Flavonoids.

## 1. Introduction

The thyroid gland is a vital component of the endocrine system and the largest endocrine gland in the body. **(Xue *et al.,* 2021).** Its primary physiological roles include controlling body metabolism and producing thyroid hormones (THs). THs and body growth and development are intimately connected. **(Beynon *et al.,* 2016 and Khan and Farhana 2022)**, and are important for the normal function of almost all tissues. Measurements of thyroid-stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), anti-thyroid peroxidase antibody (TPOAb), and anti-thyroglobulin antibody (TgAb) can all be used to track thyroid function, which is a collective indicator of TH levels. Thyrotropin-releasing hormone (TRH) and TSH regulate FT3 and FT4 through negative feedback to keep blood levels normal. **(Pirahanchi *et al.,* 2023).** Thyroid disease has become much more common in recent years. Thyroid nodule incidence has risen from approximately 10% to 20% **(McAninch *et al.,* 2019).**

A thyroxine hormone shortage is the cause of the very frequent medical disease known as hypothyroidism. The hormone thyroxine controls the body's metabolism, and a lack of it can lead to issues with a number of organ systems. If left untreated, it could have a serious negative impact on the body's health and eventually result in mortality **(Zamwar and Muneshwar 2023)**. Blood levels of thyroid-stimulating hormone (TSH) are elevated in primary hypothyroidism, meaning that they are greater than normal. Additionally, blood concentrations of free thyroxine (FT4) are lower than usual **(Salerno *et al.,* 2016).**

According to **Schellack (2013),** carbimazole (CZ) is one of the medications that can cause hypothyroidism and is essential for doing so because of its active form, methimazole (1-methyl-2-mercaptoimidazole), which prevents tyrosine from being iodinated, a process that is catalyzed by thyroid peroxidase and lowers the amount of thyroid hormones in the blood. Accordingly, experimental hypothyroidism has been induced with carbimazole **(Ahmed, 2019)** It is advised to enhance and strengthen the thyroid and the hypothalamus-pituitary-thyroid (HPT) axis's effectiveness against numerous diseases by consuming marine organisms due to their high protein, polyunsaturated fatty acid, antioxidant, micronutrient, and iodine content **(Choi and Kim, 2014;Sarkar and Pal, 2014)**. One of the most significant marine medicinal foods, Laminaria japonica is a rich source of several functional chemicals that have been extensively studied through both in vitro and in vivo investigations **(Zhao *et al.,* 2018)**. Polyphenols, fatty acids, carotenoids, steroidal ketones, amine, sterols, and tocopherol were found in Laminaria japonica, according to a number of phytochemical studies **(Han *et al.,* 2011 and Nishizawa *et al.,* 2003).**

One of the most prevalent carotenoids and the main functional pigment found in *Laminaria japonica*, fucoxanthin has been shown to possess cytoprotective, anti-inflammatory, antioxidative, and anti-obesity qualities **(Kang *et al.,* 2018)**. *Laminaria japonica* (LJ) is an essential source of dietary fiber production and a rich supply of minerals, dietary fiber, and algae **(Wang *et al.,* 2022)**. According to **Bu *et al.,* (2010)**, polysaccharides such as fucoidan, laminarin, and alginate are the main active ingredients of *L. japonica*. *Laminaria japonica* polysaccharides (LJP) have been shown in recent research to possess a variety of biological characteristics, such as anti-apoptotic, antiviral, anticoagulant, anticancer, antithrombotic, anti-radiation, hypoglycemic, hypolipidemic, and immunostimulatory effects **(Xu *et al.,* 2021).** In addition to the numerous health benefits of seaweed, this kelp is also regarded as a highly rich source of iodine, with 2353_g/g of iodine. Iodine is a necessary component of thyroid hormones, and variations in iodine consumption can induce a variety of thyroid diseases **(Nagataki, 2008).**This study was done to assess the possible preventative effect of various doses of *Laminaria japonica* ethanolic extract (LJEE) on carbimazole-induced hypothyroidism in male rats. This will be accomplished through the evaluation of serum TSH, T4, T3, and IL-6 as well as lipid profile, antioxidant indicators, and liver function. In addition, histological exams of the thyroid gland will be performed in all groups.

## 2. Material and methods

### 2.1. Materials

#### *2.1.1.* Kombu *(Laminaria japonica )*

In the winter of 2023, *Laminaria japonica* (L. japonica) powder was purchased from the Egyptian market.

#### 2.1.2. Regents ,chemicals and kits

NeoMercazol, a brand of commercial tablets containing carbimazole, was acquired from Chemical Industries Development. The supplier of biochemical assay kits was Alkan Medical Company located in St. El Doky, Giza, Egypt. The El-Gomhoreya Company in Cairo, Egypt provided all further chemicals and reagents used in this investigation. These materials were of analytical grade or the purest form currently offered for sale.

#### 2.1.3. Animals

Thirty adult male albino rats, weighing 130±10 g, were retrieved from the National Research Center's animal housing unit in Giza, Egypt. The animals were kept in a room with a controlled temperature (24°C) and standard laboratory conditions (12 hours of light and 12 hours of darkness) throughout the experiment. Rats were fed basal diet and allowed unfettered access to tap water.

### 2.1.4. Standard/Basal Diet(BD)

The **AIN (1993)** technique was followed in the preparation of the basal diet.The salt mixture utilized was prepared in accordance with **Hegsted *et al.*, (1941)**, however the vitamin mixture was added in accordance with the protocol set forth by **Campbell (1963)**. El-Gomhoriya Company for Trading Drugs, Chemicals, and Medical Instruments was the source of the diet contents that were bought.

## 2.2. Methods

### 2.2.1. *Laminaria japonica* Ethanolic Extract

500 grams of *Laminaria japonica* powder were steeped in 5000 ml of methanol 80% and the mixture was then kept in a shaker incubator for 24 hours at room temperature. then filtered through filter paper and centrifuged at 3000 rpm for 15 min. The filtrate was placed in a rotary vacum evaporator to evaporate alcohol from it, to obtain a dried powder as described by **(Mukhtar and Ghori, 2012). Machu e*t al.*, (2015)** found that extraction by 80% methanol (extraction/3/) and 100% methanol (extraction/5/), respectively, were the most efficient methods to extract phenolic compounds from *Laminaria japonica*

### 2.2.2. Quantitative determination of phenolic compounds by HPLC

The total phenolic content of the samples was determined using the Folin-Ciocalteu method **(Eom *et al.*, 2012)**. An Agilent 1260 series was used for the HPLC analysis. Zorbax Eclipse Plus C8 column (4.6 mm x 250 mm i.d., 5 μm) was used for the separation. Water (A) and 0.05% trifluoroacetic acid in acetonitrile (B) were combined to form the mobile phase, which was flowing at a rate of 0.9 ml/min. The following was the sequential linear gradient programming for the mobile phase: 18–22 min (82% A); 22–24 min (82% A); 0–1 min (82% A); 1–11 min (75% A); 11–18 min (60% A); and 0 min (82% A). At 280 nm, the multi-wavelength detector was observed. For every sample solution, there was one injection volume of five microliters. At 40°C, the column temperature was kept constant.

### 2.2.3. Experimental design

This biological experiment carried out complies with the National Research Council's **(NRC,1996)** Institute of Laboratory Animal Resources Commission on Life Sciences decisions. Following the seven-day acclimatization period, rats (n=30), were randomly assigned to five groups of six rats per group. Group 1: served as the control group and was fed on the BD, group 2: acted as the treated group, was treated orally with carbimazole by using the intragastric tube in a dose of 1.35 mg/Kg/day dissolved in 1ml distilled water (this dose is equivalent to the human therapeutic dose) following the method described by **Hashem *et al.*, (2016)**, while groups (3-5) received LJEE at concentrations of 100, 200 and 300 mg/kg bw/d, followed by the carbimazole medication 1 hour later at the same previous dose by oral gavage for 21 days. At the end of experiment, after a 12-hour fast, the rats were weighed and sedated using ether inhalation. In order to measure the biochemical parameters as stated by **Stroev and Makarova (1989)**, blood samples were taken through the abdominal aorta and put into centrifuge tubes. The serum was then properly separated following centrifugation at 3000 rpm for 10 minutes. Right and left thyroid glands were excised via a transverse incision in the upper region of the neck. This gland was revealed when the skin on one side of the face was reflected. After being cut off from the surrounding tissue, the thyroid glands were processed for histological analysis and weighed on a portable, small digital LCD electronic scale.

**2.2.3. Biochemical Analysis**

According to **Moss *et al.,* (1999)** and **Reitman *et al.,* (1957)**, several examined parameters in serum were determined using the particular procedures as follows: **liver functions analysis**, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) were measured using the lipid profile markers in accordance with the protocols outlined by **Demacker *et al.,* (1980), Allain *et al.,* (1974), and Fossati and Prencipe (1982)**. Furthermore, the following formulas were used to calculate low-density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL-c), as described by **Lee and Nieman (1996)**:

**VLDL-c =** TG/5 **, LDL-c =** Total Cholesterol - (HDL-c + VLDL-c)

Superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) were the antioxidant markers that were evaluated in accordance with **Ohkawa *et al.,* (1979), Nishikimi *et al.,* (1972), and Aebi (1984)**, respectively. At the Tumor Markers Oncology Research Center, Al-Azhar University, thyroid hormone markers (total T3, total T4) and thyroidstimulating hormone (TSH) were assessed quantitatively using in vitro diagnostic radioimmunoassay using the Immunolite 2000 analyzer **(El-Wakf *et al.,* 2009).** Using a colorimetric technique, the quantity of follicle-stimulating hormone (FSH) was measured using a rat FSH ELISA Kit from Novus Biologicals (KA2330) **(Selim, 2013).** Using competitive radioimmunoassay techniques, the concentrations of free triiodothyronine (FT3) and free thyroxine (FT4) in serum were determined **(Paczkowska *et al.,* 2020 and Henning *et al.,* 2014).** According to **Norazlina *et al.,* (2010)**, quantitative noncompetitive sandwich ELISA test kits (Market, San Jose, CA) were used to quantify interleukin-6 (IL-6) in serum. **Qin and Qiu (2019)** described a colorimetric method for determining tumor necrosis factor-α (TNF-α).

### 2.2.4. Histological Procedures

Thyroid gland specimens were obtained, and the procedure was carried out in accordance with **Banchroft *et al.*, (1996)** instructions.

### 2.2.5. Statistical analysis

The mean ± SD was used to express all values. A one-way analysis of variance (ANOVA) was used to statistically examine any significant differences between the groups. *P-values* of less than 0.05 were regarded as statistically significant.

## 3. Result and discussion

### 3.1. HPLC analysis for phenolic compounds of *Laminaria Japonica* .

Table 1 showed the identification and quantification of phenolic compounds in *Laminaria Japonica* by HPLC. Data indicated that plant have a high concentration of gallic acid, ellagic acid, kaempferol, chlorogenic acid, hesperetin, coffeic acid, rosmarinic acid, methyl gallate, vanillin, querectin, and cinnamic acid which were 7.66, 0.49, 0.42, 0.35, 0.20, 0.18, 0.13, 0.08, 0.07, 0.05, and 0.02 µg/ml respectively**.**

**Table (1): Phenolic compounds of *Laminaria Japonica*.**

| **Phenolic compounds** | **Conc. (µg/ml)** | **Phenolic compounds** | **Conc. (µg/ml)** |
|---|---|---|---|
| Gallic acid | 7.66 | Vanillin | **0.07** |
| Chlorogenic acid | 0.35 | Ferulic acid | **0.00** |
| Catechin | 0.00 | Naringenin | **0.00** |
| Methyl gallate | 0.08 | Rosmarinic acid | **0.13** |
| Coffeic acid | 0.18 | Daidzein | **0.00** |
| Syringic acid | 0.00 | Querectin | **0.05** |
| Rutin | 0.00 | Cinnamic acid | **0.02** |
| Ellagic acid | 0.49 | Kaempferol | **0.42** |
| Coumaric acid | 0.00 | Hesperetin | **0.20** |

### 3.2. Effect of LJEE (*Laminaria japonica* ethanolic extract) on BWG, FI and FER in rats with hypothyroidism:

Table 2 illustrates the effect of LJEE on BWG, FI and FER in rats with hypothyroidism. It was observed that the treated group (rats with hypothyroidism) had a significant increase in the BWG, FI and FER as compared to the normal rats, this increase was 144.88%, 15.08 % and 110.53%, respectively. This increase in biological levels because rats which treated with carbimazole had a decrease in thyroid hormones so metabolic rate was decreased and they had an increase in appetite and consequently an increase in body weight gain. Our results are in agreement with **Hayat *et al.*, (2016)** who showed that hypothyroidism induced by CZ increased in the body weight of the experimental albino rats. **Mahran *et al* (2022)** observed that rats treated with carbimazole had moderate weight gain. Supplementation with different concentrations of LJEE significantly ($P \leq 0.05$) showed a significant decrease in BWG, FI and FER compared to the positive control group ($P \leq 0.05$). The highest mean value was recorded for group (5) which fed on 300mg LJEE /kg bw. In the same table there are a significant differences observed in BWG, FI and FER between all supplemented groups. The decrease in biological levels indicates that *L. japonica* has potential as a strong antiobesity drug since LJEE modulates the lipid metabolism by decreasing activity in lipogenesis and increasing fatty acid oxidation. This results in line with those of **(Jang and Choung 2013; Kim *et al.*, 2018)** who showed that *L. japonica* extract (LJE) significantly reduced the body weight gain, food intake, HD-induced obese rats. suggesting that *L. japonica* regulates food intake and energy metabolism **(Sun and Young, 2013)**. According to **Oh *et al.*, (2016)**, LJPS showed anti-inflammatory and anti-obesity properties in rat fed a high-fat diet (HFD).

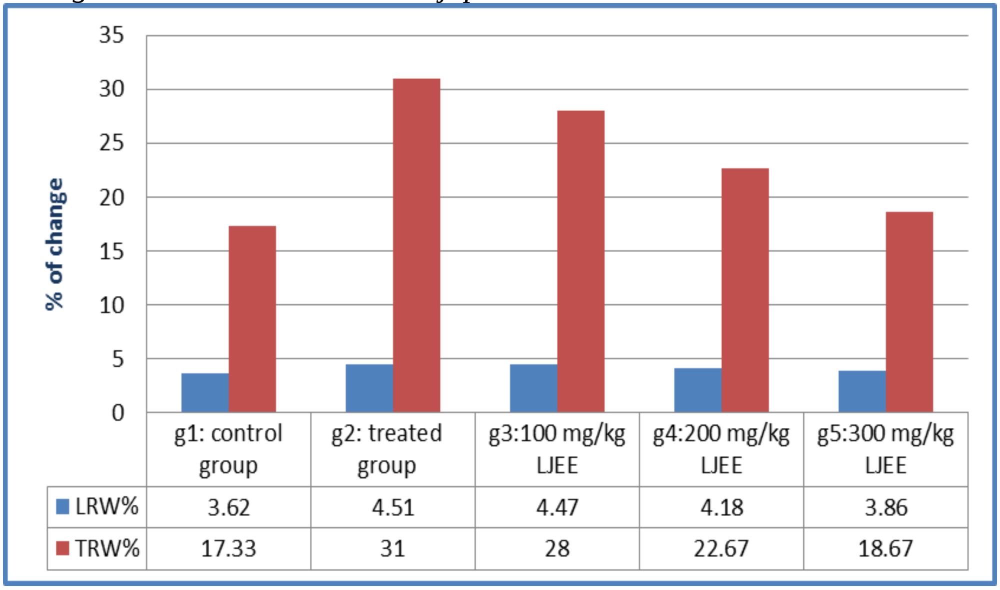
**Table (2): Effect of LJEE on BWG, FI and FER in rats with hypothyroidism**

| Parameters / Groups | BWG(g/21day) | | FI(g/day) | | FER | |
|---|---|---|---|---|---|---|
| | mean±SD | Change % | mean±SD | change% | mean±SD | change% |
| **G1:control group** | $31.17^{e}\pm1.04$ | 0.00 | $11.67^{c}\pm0.25$ | 0.00 | $0.095^{c}\pm0.005$ | 0.00 |
| **G2: treated group** | $76.33^{a}\pm0.58$ | 144.88 | $13.43^{a}\pm0.21$ | 15.08 | $0.20^{a}\pm0.03$ | 110.53 |
| **G3: 100 mg/kg LJEE** | $61.00^{b}\pm1.00$ | -20.09 | $13.17^{a}\pm0.15$ | -1.94 | $0.165^{b}\pm0.04$ | -17.5 |
| **G4: 200 mg/kg LJEE** | $44.19^{c}\pm4.17$ | -42.11 | $12.60^{b}\pm0.26$ | -6.20 | $0.125^{d}\pm0.003$ | -37.5 |
| **G5: 300 mg/kg LJEE** | $28.29^{d}\pm0.54$ | -62.93 | $12.03^{c}\pm0.15$ | -10.42 | $0.084^{e}\pm0.001$ | -58 |

Values are expressed s mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$). **BWG:** body weight gain. **FI:** feed intake. **FER:** feed efficiency ratio.

### 3.3. Effect of LJEE on LRW% and TRW% in rats with hypothyroidism.

Figure 1 reflects the effect of LJEE on LRW% and TRW% in rats with hypothyroidism. It was noticed that the treated group (rats with hypothyroidism) had a significant increase in the LRW% and TRW% as compared to the negative normal rats, this increase was 24.59% and 78.88%, respectively. This increase in biological levels is caused by the conversion of carbimazole to methimazole, the active form, following absorption. Methimazole lowers the synthesis of the thyroid hormones T3 and T4 by preventing the thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin **(Nayak and Burman 2006)**. Nodular goiter is a condition when the thyroid gland experiences hyperplasia and hypertrophy of follicular cells due to an increase in thyroid-stimulating hormone (TSH) **(Fountoulakis *et al.*, 2007)** and **(Zbucki *et al.*, 2007).** According to **Ajayi and Akhigbe (2018)**, hypothyroidism was linked to a substantial ($P < 0.05$) increase in liver weight and diameter. Supplementation with different concentrations of LJEE significantly ($P \leq 0.05$) showed a significant decrease in LRW% and TRW% compared to the positive control group ($P \leq 0.05$). There are significant differences in TRW% between all treated groups. The highest change value was recorded for group 5. This improvement is due to the high content of iodine and antioxidants in LJEE. Our results agreed with **Inui *et al.*,(2010) and Mohibbullah *et al.*, (2019)** who found that thyroid size returned to a normal level. Significant decreases in absolute and relative weights of hepatic and thyroid when administration with *Astragalus membranaceus* and *L. japonica*.




Values are expressed as mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$). **LRW**: liver relative weight. **TRW**: thyroid relative weight.

**Figure 1. Effect of LJEE on LRW% and TRW% in rats with hypothyroidism**

### 3.4. Effect of LJEE on FT3, FT4 and TSH in rats with hypothyroidism.

Table 3 showed the effect of LJEE on FT3, FT4 and TSH in rats with hypothyroidism. It was observed that the treated group had a significant decrease in the FT3 and FT4 as compared to the normal rats. The reduction of thyroid hormone levels is due to the action of CZ which inhibits iodination of tyrosine in the thyroid gland and as a consequences the concentration of TSH was elevated by a positive feed-back effect on hypophysis **(Nayak and**

**Burman 2006; Hameed *et al*., 2022; Hussein *et al*., 2022; Fekry *et al*., 2023 and Bordbar *et al*., 2024).** Supplementation with different concentrations of LJEE significantly ($P \leq 0.05$) showed a significant increase in FT3 and FT4 and a significant decrease in TSH as compared to the positive control group ($P \leq 0.05$). The highest mean values of FT3 and FT4 and the lowest mean value of TSH recorded to the group fed on 300mg LJEE/kg. Our findings concur with those of **Siahaan *et al*., (2018)**, who found that brown seaweeds—especially those of the species Laminaria, which have the ability to store iodine are a source of the mineral. It is a crucial trace element required for the synthesis of thyroid hormones, T3 and thyroxine, which support healthy bodily growth and metabolic control. Iodine from brown seaweed has a high bioavailability, ranging from 31 to 90% **(Blikra *et al*., 2022)**. Because of its high iodine content which is necessary for the creation of thyroid hormone **Jang and Choung (2013)** discovered that *L. japonica* can be used to treat hypothyroidism or thyroid nodules. In the groups getting carbimazole medication, TSH hormone levels increased and T3 and T4 hormone levels decreased **(Hadi and Hamza 2021)**.

**Table(3): Effect of LJEE on FT3, FT4 and TSH in rats with hypothyroidism**

| Parameters / Groups | FT3(ng/dl) | | FT4(ng/dl) | | TSH(µg/dl) | |
|---|---|---|---|---|---|---|
| | mean±SD | Change % | mean±SD | Change % | mean±SD | Change % |
| G1:control group | $20.73^{a}\pm0.16$ | 0.00 | $30.37^{a}\pm1.06$ | 0.00 | $6.75^{e}\pm0.21$ | 0.00 |
| G2: treated group | $8.81^{e}\pm0.06$ | -57.50 | $15.21^{e}\pm0.20$ | -49.92 | $16.36^{a}\pm0.39$ | 142.22 |
| G3: 100 mg/kg LJEE | $10.49^{d}\pm0.34$ | 19.07 | $17.98^{d}\pm0.23$ | 18.21 | $14.53^{b}\pm0.16$ | -11.19 |
| G4: 200 mg/kg LJEE | $14.62^{c}\pm0.14$ | 65.95 | $21.98^{c}\pm0.78$ | 44.51 | $12.19^{c}\pm0.56$ | -25.49 |
| G5: 300 mg/kg LJEE | $18.79^{b}\pm0.15$ | 113.28 | $28.24^{b}\pm0.67$ | 85.67 | $8.44^{d}\pm0.11$ | -48.41 |

Values are expressed as mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$). **FT3 :**Free triiodothyronine, **FT4:** free thyroxine, **TSH**: thyroid stimulating hormone.

### 3.5. Effect of LJEE on TT3, TT4 and Iodine in rats with hypothyroidism.

Table 4 illustrateds the effect of LJEE on TT3, TT4 and Iodine in rats with hypothyroidism. It was observed that the treated group had a significant decrease in the TT3, TT4 and iodine as compared to the normal rats, This results agree with CZ was decreased TT3 and TT4 and increased TSH in serum **(Osama *et al*., 2024)**. Supplementation with different concentrations of LJEE significantly ($P \leq 0.05$) showed a significant increase in TT3, TT4 and iodine compared to the positive control group ($P \leq 0.05$). The highest mean value was recorded to group 5 which fed on 300mg/kg bw from LJEE. In the same table there are a significant differences were observed in TT3, TT4 and iodine between all supplemented groups. This increase in thyroid hormones and iodine due to high content of iodine in *L. japonica*, which is necessary for the production of thyroid hormones. Our results are in agreement with **(Clark *et al*., 2003)** they demonstrated that basal and poststimulation TSH are dramatically increased by short-term dietary supplementation with *L. japonica*. It has many therapeutic and nutritional benefits. Also, it has a high content of iodine, minerals, antioxidants, proteins, fiber and complex carbohydrates. Owing to the high iodine content of *L. japonica*, eating it may raise thyroid hormone levels, depending on the amount consumed **(Gherbon *et al*., 2019)**. Thyroid hyperfunction may result from eating seaweed or dietary supplements containing seaweed **(Hagen, 2009)**.

**Table(4): Effect of LJEE on TT3, TT4 and Iodine in rats with hypothyroidism**

| Parameters / Groups | TT3 (ng/ml) | | TT4 (µg/dl) | | Iodine (µg/dl) | |
|---|---|---|---|---|---|---|
| | mean±SD | Change % | mean±SD | Change % | mean±SD | Change % |
| **G1:control group** | $67.30^{a}$±1.44 | 0.00 | $75.49^{a}$±0.84 | 0.00 | $0.189^{a}$±0.009 | 0.00 |
| **G2: treated group** | $34.77^{e}$±0.32 | -48.34 | $42.94^{e}$±0.72 | -43.12 | $0.11^{d}$±0.006 | -41.79 |
| **G3: 100 mg/kg LJEE** | $45.34^{d}$±0.98 | 30.39 | $55.66^{d}$±1.10 | 29.62 | $0.13^{c}$±0.01 | 18.18 |
| **G4: 200 mg/kg LJEE** | $56.47^{c}$±0.68 | 62.41 | $63.58^{c}$±1.00 | 48.07 | $0.147^{b}$±0.006 | 33.64 |
| **G5: 300 mg/kg LJEE** | $63.47^{b}$±1.008 | 82.54 | $71.49^{b}$±0.99 | 66.49 | $0.176^{a}$±0.006 | 60 |

The values are mean ± standard deviation. There is no statistically significant difference ($p \leq 0.05$) between values in the same row that have the same superscript letters. **TT3:** total Triiodothyronine**, TT4** :total Thyroxine

## 3.6.Effect of LJEE on SOD, CAT and MDA in rats with hypothyroidism

Table 5 illustrateds the effect of LJEE on SOD, CAT and MDA in rats with hypothyroidism. It was observed that the treated group had a significant decrease in the SOD and CAT and a significant increase in MDA level as compared to the normal rats. This change is due to oxidative stress induced by carbimazole. This results are in agreement with **Ayuob *et al*., (2019)** and **Di Domenico *et al*., (2019)** who concurred with our findings, hypothyroidism caused a rising in the production of plasma MDA and a decrement in the activity of plasma SOD this caused the development of oxidative stress in hypothyroidism leading to a devastation of cells. But This finding was disagreement with **ALKhyatt and Al Neaimy (2022)** who demonstrated that carbimazole have reduced the level of MDA.The same table represented supplementation with different concentration of LJEE significantly ($P \leq 0.05$) showed a significant increase in SOD and CAT compared to the positive control group. In addition to, hypothyroidism rats treated by LJEE had a significant increase in the MDA level as compared to positive control group. This results are in agreement with **Choi *et al*., (2011)** who demonstrated that seaweed polysaccharides, such as laminarin and fucoidan have antioxidant properties. **Long *et al*., (2012)** kelp dramatically raised the activity of serum antioxidant enzymes (CAT) and SOD significantly and decreased the level of serum MDA **(Lee *et al*., 2022;Wang *et al*., 2024 and Huang *et al*., 2021).**

**Table(5): Effect of LJEE on SOD, CAT and MDA in rats with hypothyroidism**

| Parameters / Groups | SOD(U-ml) | | CAT (ng-ml) | | MDA(nmol-ml) | |
|---|---|---|---|---|---|---|
| | mean±SD | Change % | mean±SD | Change % | mean±SD | Change % |
| **G1:control group** | $140.12^{a}\pm0.62$ | 0.00 | $8.59^{a}\pm0.28$ | 0.00 | $0.85^{e}\pm0.009$ | 0.00 |
| **G2: treated group** | $58.36^{e}\pm0.96$ | -58.35 | $3.37^{e}\pm0.14$ | -60.77 | $2.62^{a}\pm0.085$ | 208.24 |
| **G3: 100 mg/kg LJEE** | $84.31^{d}\pm1.03$ | 44.47 | $4.33^{d}\pm0.11$ | 28.49 | $2.17^{b}\pm0.072$ | -17.18 |
| **G4: 200 mg/kg LJEE** | $108.21^{c}\pm1.4$ | 85.42 | $5.26^{c}\pm0.17$ | 56.08 | $1.73^{c}\pm0.208$ | -33.97 |
| **G5: 300 mg/kg LJEE** | $134.43^{b}\pm0.64$ | 130.35 | $7.39^{b}\pm0.30$ | 119.29 | $1.18^{d}\pm0.035$ | -54.96 |

The values are mean ± standard deviation. There is no statistically significant difference ($p \leq 0.05$) between values in the same row that have the same superscript letters. **SOD:** Superoxide dismutase, **CAT:** Catalase, **MDA:** Malondialdehyde.

## 3.7.Effect of LJEE on AST, ALT and ALP in rats with hypothyroidism

Table 6 presents the effect of LJEE on AST, ALT and ALP in rats with hypothyroidism. There were a significant increase in AST, ALT and ALP as compared to the normal rats. This increase was 74.26%, 77.81% and 87.89%. This increase is due to the liver dysfunction induced by carbimazole and the effect of thyroid dysfunction may perturb liver function. This fresults align with **Lashein *et al*., (2022)**; **Hashem *et al*., (2016); Abdelmoneim, 2020, and Abdullah *et al*., 2024 whose** reported that there were a significant increase in ALT and AST activities in the hypothyroid group induced by carbimazole**.** Furthermore,there was a significant increase in serum AST and ALT enzyme levels in groups treated by carbimazole when compared with control**.** Similar results also were observed by **Sakr *et al*., (2015)** who suggested that hypothyroidism caused hepatocyte damage because of free radicals and the inability of antioxidants to resist an increase in free radicals. According to **Papachristos *et al.*, (2015)**, the significant cholestatic liver damage was caused by the carbimazole therapy; additionally, the type of liver damage, the time after the start of the carbimazole, and the presence of intrahepatic cholestasis suggested that the carbimazole was the cause of an adverse drug reaction.. Supplementation with LJEE with different concentration significantly ($P \leq 0.05$) showed a significant decrease in AST, ALT and ALP compared to the positive control group ($P \leq 0.05$). The best mean value was recorded to the group which fed on LJEE 300mg/kg**.** In the same table described a significant differences were observed in AST, ALT and ALP between all treated groups. This decrease in liver enzymes due to LJEE high content from antioxidants witch protects the liver from oxidative stress and improves its functions. These results were in line with those of **Meenakshi *et al.*, (2014)** who found that fucoidan, a polysaccharide derived from *L. japonica*, is believed to have hepatoprotective effects because of its antioxidant properties. **Kang *et al*., 2006)**. **Zhang *et al*., (2016)** reported that the insoluble dietary fiber of LJPS decreased the level of ALT and AST. Also, **Sun and Young (2013)** and **Jiang *et al*., (2013)** indicated that *L. japonica* was not associated with any damage to the liver and renal.

**Table(6): Effect of LJEE on AST, ALT and ALP in rats with hypothyroidism**

| Parameters / Groups | AST(U/L) | | ALT(U/L) | | ALP(U/L) | |
|---|---|---|---|---|---|---|
| | **mean±SD** | **Change %** | **mean±SD** | **Change %** | **mean±SD** | **Change %** |
| **G1:control group** | $80.34^{e}\pm1.37$ | 0.00 | $63.71^{e}\pm1.76$ | 0.00 | $97.09^{e}\pm1.33$ | 0.00 |
| **G2: treated group** | $140.28^{a}\pm1.74$ | 74.26 | $113.28^{a}\pm1.98$ | 77.81 | $182.43^{a}\pm1.13$ | 87.89 |
| **G3: 100 mg/kg LJEE** | $114.09^{b}\pm1.38$ | -18.67 | $93.33^{b}\pm1.64$ | -17.61 | $132.03^{b}\pm1.70$ | -27.63 |
| **G4: 200 mg/kg LJEE** | $99.93^{c}\pm0.59$ | -28.76 | $76.72^{c}\pm1.62$ | -32.27 | $112.17^{c}\pm0.65$ | -38.51 |
| **G5: 300 mg/kg LJEE** | $88.39^{d}\pm0.75$ | -36.99 | $67.30^{d}\pm1.21$ | -45.00 | $100.42^{d}\pm1.78$ | -44.95 |

The values are mean ± standard deviation. There is no statistically significant difference ($p \leq 0.05$) between values in the same row that have the same superscript letters**. AST** aspartate aminotransferase, **ALT:** Alanine transaminase; **ALP**: Alkaline phosphatase

## 3.8. Effect of LJEE on serum lipid and lipoprotein profiles in rats with hypothyroidism

Table 7 reflects the effect of LJEE on serum lipid and lipoprotein profiles in rats with hypothyroidism. There were a significant increase in T.C, T.G, LDL, and VLDL as compared to the normal rats, This increase is due to carbimazole action which decreased thyroid hormones which control fat metabolism and it̕ s decreased activity of lipoprotein lipase. Similar results were also observed by **Hennemann *et al*., (2001); Afaf, (2015); Saleh, (2015)** and **Evagelos and Moses (2002). Also,** These results are parallel with **Hameed *et al*., (2022), Nasser *et al*., (2021) and Abdullah *et al*., (2024)** they reported that the level of TG, LDL, and VLDL were increased, while, the level of HDL was decreased after the treatment with CZ. Supplementation with LJEE with different concentration significantly (P≤0.05) showed a significant decrease in T.C, T.G, LDL, and VLDL compared to the positive control group (P≤0.05) . The best treatment was recorded for the group that fed LJEE 300mg/kg BW**.** Also**,** a significant differences were observed in T.C, T.G, LDL, and VLDL between all treated groups. This improvement is related to dietary mannogluconic acid (MA) and fucogalactan sulfate (FS) two purified polysaccharides and fucoidan derived from *L. japonica* whose improve lipid metabolism disorders. This results in agreement with **Fang *et al*., (2023); Shang *et al*., (2017) and Lu *et al*., (2024).** The extract from *L. japonica* prevents the accumulation of body fat, leading to improve lipid profiles in serum, decreased the levels of serum TG, TC, and LDL-c. It elevate (HDL-c), **(Jang and Choung 2013).** This improvement in lipid profile due to *L. japonica* extract inhibits the accumulation of body fat, resulting an improve in lipid profiles in serum **(Sun and Young 2013** and **Aoe *et al*., 2021)**. Also, According to **Zheng *et al*., (2018)**, a sulfated polysaccharide derived from brown seaweeds known low molecular weight fucoidan (LMWF) decreased TC and TG in mice as well as the amount of TG and TC that accumulated in their livers.

**Table(7): Effect of LJEE on serum lipid and lipoprotein profiles in rats with hypothyroidism**

| Parameters / Groups | T.C (mg/dl) | T.G (mg/dl) | HDL-c (mg/dl) | LDL-c (mg/dl) | VLDL-c (mg/dl) |
|---|---|---|---|---|---|
| | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD |
| **G1:control group** | $120.58^{e}$±1.46 | $87.94^{e}$±1.93 | $53.28^{a}$±1.05 | $49.72^{e}$±0.58 | $17.59^{e}$±0.38 |
| **G2: treated group** | $208.09^{a}$±0.66 | $177.58^{a}$±2.53 | $39.52^{e}$±0.83 | $133.06^{a}$±1.61 | $35.52^{a}$±0.51 |
| **G3: 100 mg/kg LJEE** | $179.04^{b}$±1.46 | $147.49^{b}$±3.14 | $42.19^{d}$±1.89 | $107.35^{b}$±2.31 | $29.49^{b}$±0.63 |
| **G4: 200 mg/kg LJEE** | $155.00^{c}$±1.70 | $134.62^{c}$±2.49 | $46.24^{c}$±0.79 | $81.84^{c}$±1.39 | $26.92^{c}$±0.5 |
| **G5: 300 mg/kg LJEE** | $128.87^{d}$±2.28 | $102.27^{d}$±2.47 | $49.81^{b}$±0.47 | $58.59^{d}$±3.2 | $20.45^{d}$±0.49 |

Values are expressed as mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$). **TC**: Total cholesterol, **TG**: Triglycerides, **HDL-c**: High-density lipoprotein cholesterol,

**LDL-c**: Low-density lipoprotein cholesterol, **VLDL-c**: Very low-density lipoprotein cholesterol.

### 3.9. Effect of LJEE on IL-6 and TNF-α in rats with hypothyroidism

Table 8 explain the effect of LJEE on IL-6 and TNF-α in rats with hypothyroidism. There were a significant increase as compared to the normal rats, this increase was 85.87% and 103.56% respectively. This increase due to the action of carbimazole, which increases oxidative stress. This results in agreement with **Zhou *et al*., (2018)** they demonstrated that hypothyroidism is probably connected with elevated levels of proinflammatory cytokines**.** There was a significant elevated in the levels of serum TNF-α and IL6 in dysthyroid animals **(Ajayi *et al*., 2018)**. The levels of TNF-α and IL-6 in hypothyroid rats showed a significant ($P < 0.001$) rise when compared with the control group **(Osama *et al*., 2024).** Supplementation with LJEE with different concentration significantly ($P \leq 0.05$) showed a significant decrease in IL-6 and TNF-α compared to the positive control group ($P \leq 0.05$). The lowest mean value was recorded to the group which fed on 300mg/kg bw LJEE**.** In the same table described a significant differences were observed in IL-6 and TNF-α between all treated groups. This improvement due to LJEE high content from antioxidants. This results agreed with **Sun and Young (2013)** who showed that *L. japonica* extract upplemented showed reduced TNF-α. TNF-α mRNA level in adipose tissue was also reduced. LJPS inhibiting the secretion of inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α, etc.) and macrophage-related chemokines **(Jia *et al*., 2014) and (Jang and Choung 2013)** and (**Lee *et al*., 2022**).

**Table (8): Effect of LJEE on IL-6 and TNF-α in rats with hypothyroidism**

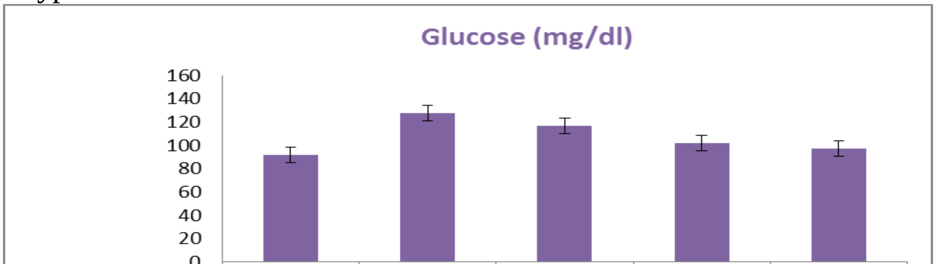
| Parameters / Groups | IL-6 (pg/mL) | | TNF-α (pg/mL) | |
|---|---|---|---|---|
| | mean±SD | change% | mean±SD | change% |
| **G1:control group** | $9.27^{e}\pm0.25$ | 0.00 | $29.77^{e}\pm1.7$ | 0.00 |
| **G2: treated group** | $17.23^{a}\pm0.68$ | 85.87 | $60.60^{a}\pm0.90$ | 103.56 |
| **G3: 100 mg/kg LJEE** | $14.53^{b}\pm0.208$ | -15.67 | $50.43^{b}\pm0.83$ | -16.78 |
| **G4: 200 mg/kg LJEE** | $12.87^{c}\pm0.153$ | -25.30 | $38.75^{c}\pm0.93$ | -36.06 |
| **G5: 300 mg/kg LJEE** | $10.50^{d}\pm0.44$ | -39.06 | $33.65^{d}\pm0.99$ | -44.47 |

Values are expressed as mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$). . **IL-6:** interleukin-6 **,TNF-α:** tumor necrosis factor alpha.

### 3.10. Effect of LJEE on glucose in rats with hypothyroidism

Results in figure (2) showed the effect of LJEE on glucose in rats with hypothyroidism. There were a significant increase in hypothyroidism groups as compared to the control group, This increase in glucose levels due to metabolism disorder of glucose. This came in agreement with **Yeldu and Ishaq (2017)** who confirmed that metabolism disorder of glucose in hyperthyroid is mainly related to oxidative stress by exerting deleterious effects on pancreas and liver, **Vazquez-Anaya *et al*. (2017)** study has confirmed that hypothyroidism is related to insulin resistance. In hypothyroidism, the mechanism of insulin resistance was attributed by the study of **Ormazabal *et al*., (2018)** who found that glucose was a significantly increased in hypothyroid groups in comparison to the control group **(Abdullah *et al*., 2024).**

Supplementation with LJEE with different concentration significantly ($P \leq 0.05$) showed a significant ($P\leq0.05$) decrease in glucose compared to the treated group ($P\leq0.05$). The best mean value was recorded to the group which fed LJEE 300mg/kg BW**.** This decrease because *L. japonica* reduces the intestinal absorption of glucose. Our findings are consistent with those of **Kang *et al*., (2018)**, **Agarwal *et al*., (2023)**, and **Lee *et al*., (2022)**, who showed that LJPS dramatically reduced fasting blood glucose levels and increased serum insulin levels, hence having an anti-diabetic impact. According to **Popović-Djordjević *et al*., (2021)**, bioactive chemicals found in algae, including brown algae, directly promote insulin production, inhibit the development of amyloid plaques, and reduce hyperglycemia in individuals with type 2 diabetes.




| | g1: Control group | g2:Treated group | g3:100mg/kg LJEE | g4:200mg/kg LJEE | g5:300mg/kg LJEE |
|---|---|---|---|---|---|
| Glucose (mg/dl) | 92 | 127.67 | 116.67 | 101.67 | 97 |

Values are expressed as mean ± SD. Different superscript letters in the same column represent statistically significant differences ($p \leq 0.05$).

**Figure2. Effect of LJEE on glucose in rats with hypothyroidism.**

### 3.11. Effect of LJEE on thyroid gland histological disorders induced by carbimazole.

Effect of LJEE on hypothyroidism rats was illustrated in Figure 3. Microscopical examination of thyroid gland of rats from Control group (g.1) revealed the normal histoarchitecture of thyroid follicles which lined by a single layer of cuboidal epithelium and their lumen are filled with homogenous eosinophilic colloidal materials (Pic.1&2). In adverse, thyroid gland of rats from treated group (g2) showed histopathological lesions characterized by marked necrosis of follicular epithelium associated with inflammatory cells infiltration, cystic dilatation of some follicles with flattened lining epithelium (Pic.3,4&5) and empty lumen of most follicles (Pic.5). Meanwhile, thyroid gland of rats from CZ+LJEE 100 group (g3) revealed dilatation of some follicles with flattened lining epithelium and their lumen distended with colloid associated with few interstitial inflammatory cells infiltration (Pic.6&7), and some normal thyroid follicles with normal cuboidal lining epithelium and eosinophilic colloid in their lumen (Pic.8). Furthermore, some examined sections from CZ+LJEE 200 group (g4) exhibited normal thyroid follicles with normal cuboidal lining and eosinophilic colloid in their lumen (Pic. 9), whereas other sections showed slight interstitial edema (Pic.10) and congested blood vessel (Pic.10&11). Likewise, some examined sections from CZ+LJEE 300 group (g5) revealed normal thyroid follicles with normal cuboidal lining epithelium and eosinophilic colloid in their lumen (Pic.12), whereas other sections exhibited cystic dilation of some thyroid follicles with flattened lining epithelium and eosinophilic colloid in their lumen (Pic.13) as well as some follicles are lined by more than one layer of follicular cells (Pic.14). These findings support the findings of **Al-shaikh *et al.*, (2014)**, who noted that in the hypothyroid group of rats treated with carbimazole, the thyroids displayed modified, enlarged (Goiter) follicles of varying sizes, filled with a variable amount of little dense and extremely vacuolated colloid. Also, **Hussein *et al.*, (2022)** reported that thyroid gland showed hyper cellularity of cuboidal epithelium in rats injected with carbimazole. According to **Kravchenko *et al.*, (2017)**, treating hypothyroid rats with *Laminaria Japonica* extract nearly entirely restored the thyroid gland's histological structure to that of healthy animals. All of these results showed that LJEE was able to partially regenerate thyroid tissue and effectively recover thyroid gland function to normal.

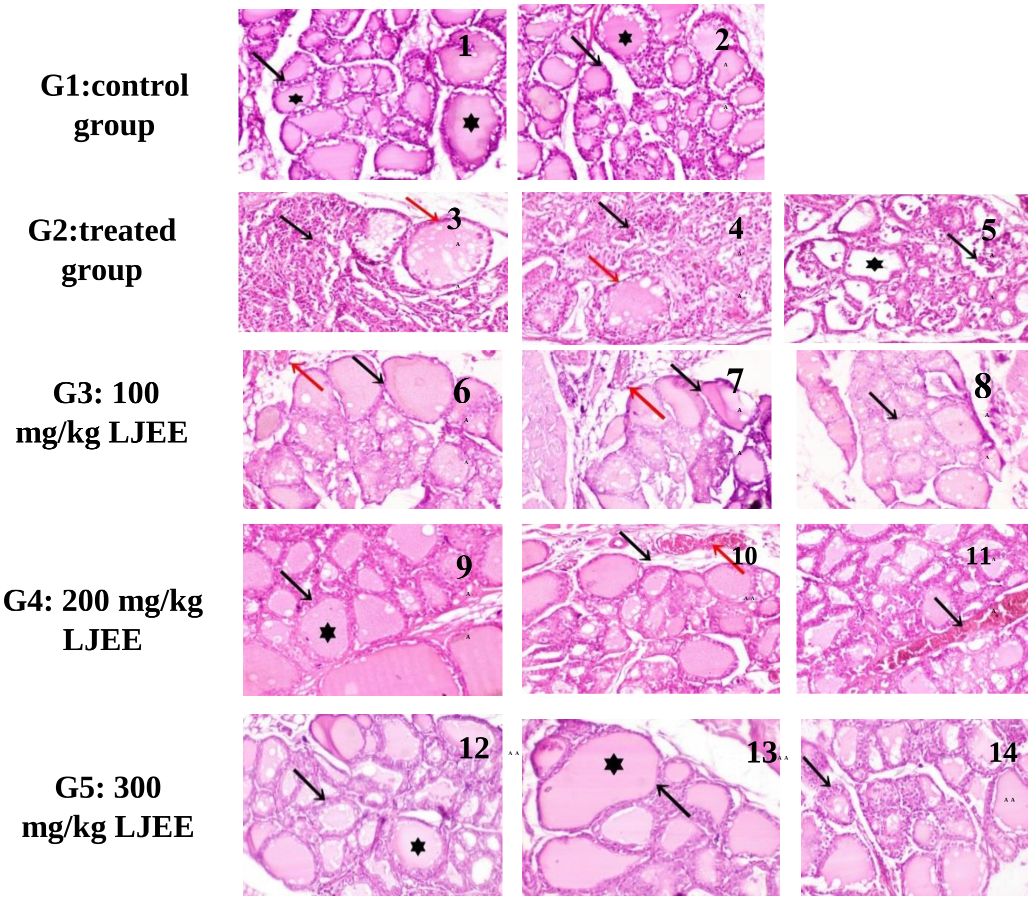



**Figure 3. Effect of *Laminaria Japonica* Ethanolic Extract (LJEE) on hypothyroidism rats . Pic 1 &2) group1**, showing normal histoarchitecture of thyroid follicles which lined by a single layer of cuboidal epithelium (black arrow) and their lumen are filled with homogenous eosinophilic colloidal materials (asterisk) (H & E X 400). **Pic. 3&4) group2**, showing marked necrosis of follicular epithelium associated with inflammatory cells infiltration (black arrow) and cystic dilatation of some follicles with flattened lining epithelium (red arrow) (H & E X 400). **Pic. 5) group2**, showing marked necrosis of follicular epithelium (black arrow) and empty lumen of some follicles (asterisk) (H & E X 400). **Pic. 6&7) group 3,** showing cystic dilatation of some follicles with flattened lining epithelium and their lumen distended with colloid (black arrow) associated with few interstitial inflammatory cells infiltration (red arrow) (H & E X 400). **Pic. 8) group 3,** showing normal thyroid follicles with normal cuboidal lining epithelium and eosinophilic colloid in their lumen (black arrow) (H & E X 400). **Pic. 9) group 4,** showing normal thyroid follicles with normal cuboidal lining

epithelium (black arrow) and eosinophilic colloid in their lumen (asterisk) (H & E X 400). **Pic. 10) group 4,** showing slight interstitial edema (black arrow) and congested blood vessel (red arrow) (H & E X 400). **Pic. 11) group 4,** showing congested blood vessel (black arrow) (H & E X 400). **Pic. 12) group 5**, showing normal thyroid follicles with normal cuboidal lining epithelium (black arrow) and eosinophilic colloid in their lumen (asterisk) (H & E X 400). **Pic. 13) group 5,** showing cystic dilation of some thyroid follicles with flattened lining epithelium (black arrow) and eosinophilic colloid in their lumen (asterisk) (H & E X 400). **Pic. 14) group 5,** showing some follicles are lined by more than one layer of follicular cells (black arrow) (H & E X 400).

## 4. Conclusion.

Carbimazole, an anti-thyroid drug which leads to experimentally induced hypothyroidism. LJEE has many therapeutic and nutritional benefits: it is a high content iodine and antioxidants, Therefore, it treats hypothyroidism and some associated changes caused by carbimazole. Based on the findings of our study, it can be concluded that LJEE can elevate the level of thyroid hormones, antioxidant enzymes (SOD and CAT) and HDL levels in serum, but it led to a lowering of the level of biological parameters (BWG, FI, FER, LRW, TRW) and some parameters in serum such as TSH, MDA, liver enzymes (AST, ALT, ALP), cytokines (TNF-α, I-6), lipid profil (TC, TG, LDL, VLDL) and glucose. Therefore, *laminaria japonica* is considered an effective treatment in treating hypothyroidism and the changes that follow.

## Ethical approval

The Institutional Animal Care and Use Committee (IACUC) at Menoufia University, Sheibin El-Kom, Egypt, has approved all experimental and animal care procedures ethically (Approval No. MUFHE/F/NFS/19/24).

## Competing interests

The authors claim to have no conflicting goals.

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# التأثير الوقائي المحتمل لمستخلص اللاميناريا جابونيكا الإيثانولي على قصور الغدة الدرقية الناجم عن الكاربيمازول في ذكور الفئران البيضاء

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**الملخص**

ينشأ قصور الغدة الدرقية عندما لا تنتج الغدة الدرقية ما يكفي من هرمونT3 و T4. إذا لم يتم علاج قصور الغدة الدرقية، فيمكن أن يسبب في النهاية مشاكل في القلب وارتفاع نسبة الكوليسترول، ومشاكل صحية أخرى. يعتبر اللاميناريا جابونيكا من أهم الأعشاب البحرية، ذات الفوائد الصحية المتنوعة، خاصة في حالات قصور الغدة الدرقية، وذلك لإحتوائها على نسبة عالية من اليود والمركبات الفينولية. لذا، هدفت هذه الدراسة إلى تقييم التأثير الوقائي المحتمل لجرعات مختلفة من مستخلص اللاميناريا جابونيكا الإيثانولي (LJEE) على قصور الغدة الدرقية الناجم عن الكاربيمازول في ذكور الجرذان. تم تقسيم ثلاثين من الفئران البيضاء الذكور إلى خمس مجموعات (6 لكل مجموعة)؛ المجموعة الضابطة (G1) ، المجموعة المعالجة (G2) تلقت 1.35 ملغم/كغم من الكاربيمازول عن طريق الفم، المجموعات (3-5) التي تلقت محلول ملحي فسيولوجي و100، 200،و300 ملغم/كجم من وزن الجسم/يوم LJEE ، على التوالي، وبعد ساعه من تناول المستخلص، تم إعطاء كاربيمازول عن طريق الفم بنفس الجرعة السابقة لمدة 21 يومًا. في نهاية التجربة تم تصويم الفئران ثم ذبحها وجمع عينات الدم والغدد الدرقية لتقييمها كيميائيا ونسيجيا. أدى علاج الجرذان بالكاربيمازول إلى انخفاض معنوي ($p\leq0.05$) في هرمونات الغدة الدرقية والإنزيمات المضادة للأكسدة(SOD ، CAT)ومستويات HDL في المصل. وعلاوة على ذلك، فإن مستويات MDA زادت بشكل ملحوظ في المجموعة المعالجة مقارنة بالمجموعة الضابطة. لم تؤدي المعالجة المسبقة للفئران باستخدام LJEE بجرعات مختلفة إلى تحسين هرمونات الغدة الدرقية ومضادات الأكسدة وإنزيمات الكبد( ALP،ALT، AST) ومستويات TSH في المصل فحسب، بل أدت أيضًا إلى انخفاض ملحوظ في مستويات السيتوكينات( -TNF α، IL-6)، وصورة الدهون (TC ، TG، LDL، VLDL) والجلوكوز في المصل كما سجل تحسنًا في كل من المعايير الجزيئية والنسيجية للغدة الدرقية. ولذلك يعتبر المستخلص الكحولي للاميناريا جابونيكا علاجا فعالا في علاج قصور الغدة الدرقية والتغيرات التي تتبعه.

**الكلمات الدالة.** هرمون الغدة الدرقية، نقص اليود، الأعشاب البحرية، مضادات الأكسدة، الفلافونويدات.