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Ameliorative Role of Aqueous Saussurea lappa Root Extract in Tamoxifen-Induced Thyroid Dysfunction in Female Rats

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الدور الوقائي للمستخلص المائي لجذور نبات القسط الهندي ضد الإختلال الدرقي المستحث بالتاموكسيفين في إناث الجرذان

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Abstract
Background: This study was designed to evaluate the protective effects of Saussurea lappa aqueous root extract (SLRE) against tamoxifen (TMX)-induced thyroid dysfunction in adult female rats. Materials and Methods: Twenty-four adult female albino rats were randomly allocated into four groups (n = 6 per group): (1) control group receiving distilled water, (2) SLRE-treated group receiving 200 mg/kg, (3) TMX -treated group receiving 40 mg/kg, and (4) combined treatment group receiving both TMX (40 mg/kg) and SLRE (200 mg/kg). All treatments were administered orally via gavage once daily for 28 consecutive days. Serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured to assess thyroid function. Results: Administration of TMX resulted in significant thyroid dysfunction, characterized by elevated serum TSH levels and reduced concentrations of FT3 and FT4 compared to the control group (p = 0.001). Co-treatment with SLRE markedly ameliorated these hormonal disturbances, restoring thyroid hormone levels towards normal values (p = 0.001). The biochemical study was confirmed by histopathological investigation Conclusion: Tamoxifen induces thyroid dysfunction in adult female rats, whereas SLRE exhibits a protective effect by modulating thyroid hormone profiles. These findings suggest the potential of SLRE as an adjunct therapeutic agent for managing tamoxifen-induced thyroid dysfunction.

Keywords: Rat, Saussurea lappa extract, tamoxifen, thyroid dysfunction, thyroxine.

الملخص
هدفت هذه الدراسة إلى تقييم التأثير الوقائي للمستخلص المائي لجذور نبات القسط الهندي (SLRE) ضد الخلل الدرقي المستحث بعقار التاموكسيفين(TMX) في إناث الجرذان. تم تقسيم أربعٍ وعشرون (24) أنثى بالغة من جرذان الألبينو بشكل عشوائي إلى أربع مجموعات (6 لكل مجموعة), مجموعة ضابطة (ماء مقطر)، مجموعة مستخلص القسط الهندي (200 ملغم/كغم) ، مجموعة التاموكسيفين (40 ملغم/كغم)، ومجموعة المعالجة المشتركة (تاموكسيفين 40 ملغم/كغم + المستخلص 200ملغم/كغم). تم إعطاء المعالجات يوميًا عن طريق التناول الفموي (التغذية الأنبوبية) لمدة 28 يومًا. جرى قياس مستويات هرمونات الغدة الدرقية في المصل TSH ، وثلاثي يودوثيرونين الحر FT3، والثيروكسين الحر FT4 لتقييم وظائف الغدة الدرقية. أدى إعطاء التاموكسيفين إلى اضطراب ملحوظ في وظائف الغدة الدرقية، حيث ارتفعت مستويات TSH في المصل وانخفضت تراكيز FT3 وFT4 مقارنةً بالمجموعة الضابطة (p = 0.001). أما المعالجة المشتركة مع SLRE فقد حسَّنت هذه التغيرات بشكل كبير، مما أعاد التوازن الهرموني إلى مستوياته الطبيعية (P=0.001) .وأكد الفحص النسيجي هذه النتائج البيوكيميائية، حيث

أظهر تحسناً في البنية النسيجية للغدة الدرقية في مجموعة المعالجة المشتركة. يُسَبِّب التاموكسيفين خللاً وظيفياً في الغدة الدرقية لدى إناث الجرذان البالغة، بينما أظهر مستخلص جذور القسط الهندي تأثيراً وقائياً عبر تعديل مستويات الهرمونات الدرقية والحفاظ على البنية النسيجية للغدة. وتشير هذه النتائج إلى إمكانية استخدام SLRE كعامل علاجي مساعد للوقاية من الخلل الدرقي الناجم عن التاموكسيفين.

الكلمات الدالة: الجرذان، التاموكسيفين، ثيروكسين، مستخلص Saussurea lappa، اختلال وظائف الغدة الدرقية.

Introduction

Tamoxifen (TMX), a synthetic anti-estrogen, is considered the primary endocrine therapy for hormone-responsive breast cancer (Furr & Jordan, 1984). Beyond its role in blocking estrogen receptors, tamoxifen also affects various biochemical pathways. Notably, it increases circulating concentrations of hormone-binding globulins such as sex hormone-binding globulin (SHBG), cortisol-binding globulin (CBG), and thyroxin-binding globulin (TBG), which is likely attributed to its partial estrogen agonist activity on hepatic protein synthesis **(Fex et al., 1981;** Sakai et al., 1978).However, its precise influence on thyroid function remains incompletely understood. Studies have documented elevated plasma levels of TBG and total thyroxin (T4) in patients receiving tamoxifen (Fex et al., 1981; Cuzik et al., 1993). Nonetheless, investigations into its effects on free thyroxine (FT4) and thyroid-stimulating hormone (TSH) have yielded inconsistent results (Gordon et al., 1986; Mamby et al., 1995).Furthermore, to date; no published data are available regarding tamoxifen's impact on thyroglobulin (TG) and free triiodothyronine (FT3).

Saussurea lappa, commonly known as "Qust Al-Hindi," is a widely recognized medicinal herb belonging to the Asteraceae family. Its dried roots have been extensively utilized in traditional medicine systems such as Ayurveda, Unani, and Chinese medicine to treat various ailments, including respiratory disorders, gastrointestinal disturbances, and endocrine imbalances (Madhuri et al., 2012).Pharmacological investigations have revealed that *S. lappa* exhibits strong antioxidant, anti-inflammatory, immunomodulatory, and hepatoprotective activities (Pandey, 2012). The herb's bioactive compounds, notably dehydrocostus lactone and costunolide, have been reported to regulate cellular redox homeostasis and inhibit inflammatory mediators, potentially contributing to the protection of endocrine organs from oxidative stress and drug-induced toxicity (Robinson et al., 2008). Furthermore, recent studies have suggested a modulatory role for *S. lappa* in hormonal regulation and thyroid
Function (Alnahdi, 2017). However, its protective effects against thyroid dysfunction induced by pharmaceutical agents such as tamoxifen remain largely unexplored. Therefore, given the known endocrine-disrupting effects of TMX and the promising protective properties of *S. lappa*, the present study aims to investigate the beneficial impact of *S. lappa* root aqueous extract (SLRE) on TMX-induced thyroid dysfunction in female rats.

Material and methods

Drugs

Tamoxifen (tamoxifen citrate), commercially known as Nolvadex®, was manufactured by AstraZeneca, United Kingdom, and provided in tablet form. For the purposes of this study, the tablets were suspended in distilled water and administered orally to the experimental animals at a dose of 40 mg/kg body weight. This dosage is equivalent to the therapeutic dose used in humans and was given once daily for 28 consecutive days, in accordance with the protocols described by (Paget, 1964)

Plant Sample Collection and Extraction Procedure

Dried roots of *Saussurea lappa* were obtained from a local medicinal plant market in Benghazi, Libya. For aqueous extraction, 1 kg of powdered root material was boiled in 5 liters of distilled water for 30 minutes and then filtered. The resulting solution was freeze-dried (lyophilized). Approximately 35 g of the dried extract was reconstituted in distilled water to prepare a final concentration of 50 mg/ml for experimental use (Saleem et al., 2013).

Experimental Animals and Treatment Protocol

Twenty-four female albino rats (eight weeks old), weighing between 180 and 190 g, were used in this study. The animals were obtained from the Animal House of the Faculty of Medicine, University of Benghazi. They were maintained under controlled environmental conditions (temperature 23–25 °C, humidity 50–65%, 12-h light/dark cycle) and provided with a standard diet and water *ad libitum*. All rats were allowed to acclimatize for seven days before the experiment, after which they were randomly assigned to four groups (n = 6 per group):

- **Group I (Control):** Received normal saline orally only.
- **Group II (SLRE):** Received *Saussurea lappa* root extract (200 mg/kg/day) orally for 28 consecutive days. (Saleem et al., 2013).
- **Group III (TMX):** Received tamoxifen suspension (40 mg/kg/day) orally for 28 consecutive days. (Paget, 1964)
- **Group IV (TMX + SLRE):** Received both tamoxifen (40 mg/kg/day) and SLRE (200 mg/kg/day) orally for 28 consecutive days.
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Blood Collection Procedure

At the end of the experimental period, the rats were anesthetized with ether vapor. Blood samples were collected and allowed to clot, and the sera were subsequently separated by centrifugation at 3000 rpm under cooling conditions. The obtained sera were stored for subsequent biochemical analyses.

Biochemical Analysis.

Serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were determined using a radioimmunoassay kit (xh6080, Xi'an).

Histopathological Preparation of the Thyroid Gland

Thyroid glands from female rats of all groups were excised, fixed in 10% neutral-buffered formalin, dehydrated in graded alcohols, cleared in xylene, and embedded in paraffin. Sections of 4–5 µm were prepared using a microtome and stained with hematoxylin and eosin (H&E) for light microscopic examination. (Bancroft & Gamble, 2008).

Statistica Analysis

The collected data were analyzed by comparing the mean values of the tamoxifen-treated groups with those of the control group. Results are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test was applied to identify statistically significant differences between groups. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 27.

Results

Serum TSH

The effect of SLRE on serum TSH levels, a key biomarker of thyroid gland function, is illustrated in **Figure 1**. No significant change in serum TSH levels was observed in rats administered SLRE alone compared to the control group. In contrast, a significant increase in TSH levels was recorded in the serum of tamoxifen (TMX)-intoxicated rats relative to the control group (P = 0.001). Notably, co-administration of SLRE with TMX markedly mitigated the elevated TSH levels, as evidenced by a significant reduction in the TMX + SLRE group compared to the TMX-only group (P = 0.001).

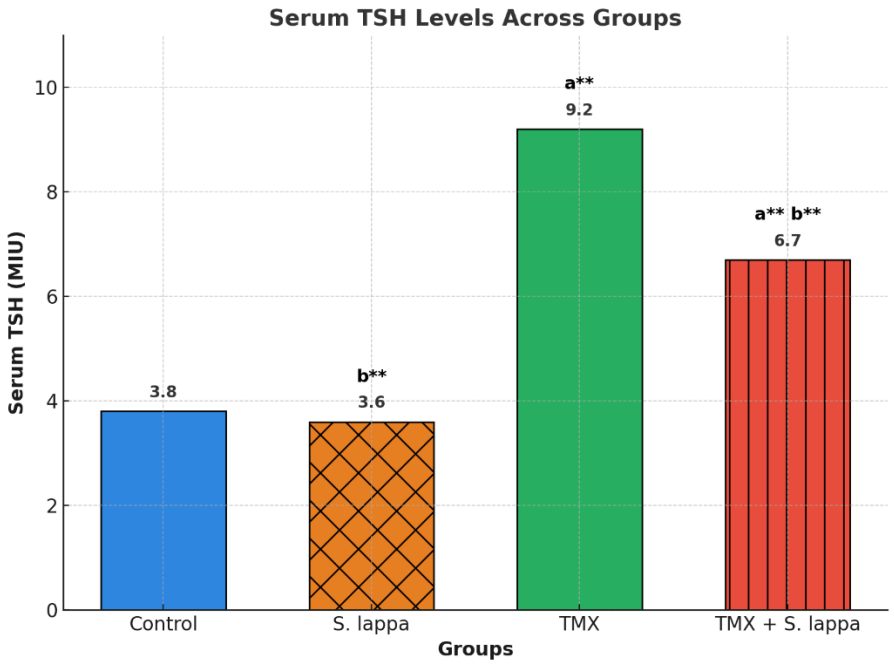

Figure1. Effect of *Saussurea lappa* root extract (SLRE) on serum TSH levels in tamoxifen (TMX)-induced hypothyroidism in rats. Values are expressed as mean ± SD of 6 rats, $^{a**}P$=0.001, compared to control, $^{b**}P$= 0.001 compared to TMX.

Serum FT3

Figure 2 shows the effect of SLRE on serum FT3 levels as an additional biomarker of thyroid gland function in the experimental animal groups. There was no significant change in FT3 levels in rats treated with SLRE alone compared to the control group. Conversely, TMX-intoxicated rats exhibited a significant decrease in serum FT3 levels relative to controls (p = 0.001). Concurrent administration of SLRE with TMX significantly increased serum FT3 levels in the TMX-SLRE group compared to the TMX group (p = 0.001).

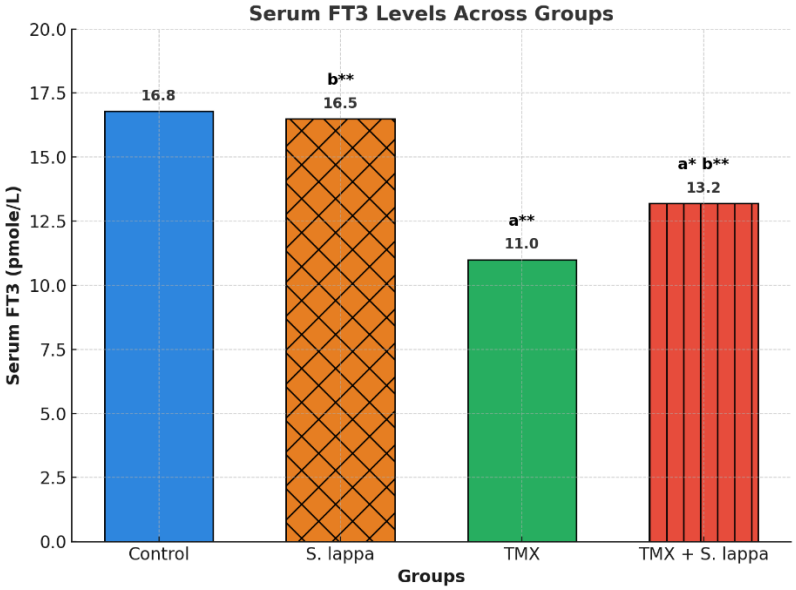

Figure2. Effect of *Saussurea lappa* root extract (SLRE) on serum FT3 levels in tamoxifen (TMX)-induced hypothyroidism in rats, $^{a**}P$=0.001, compared to control, $^{b**}P$= 0.001 compared to TMX.

Serum FT4

Figure 3 shows the influence of SLRE on serum FT4 levels as an indicator of thyroid gland function in different animal groups. A significant decrease in serum FT4 was observed in rats treated with SLRE alone compared to controls ($p < 0.05$), while TMX-intoxicated rats exhibited a severe depletion of this thyroid hormone relative to controls ($p = 0.001$). Concurrent administration of SLRE with TMX significantly up regulated serum FT4 levels in the TMX-SLRE group compared to the TMX-only group ($p = 0.001$)

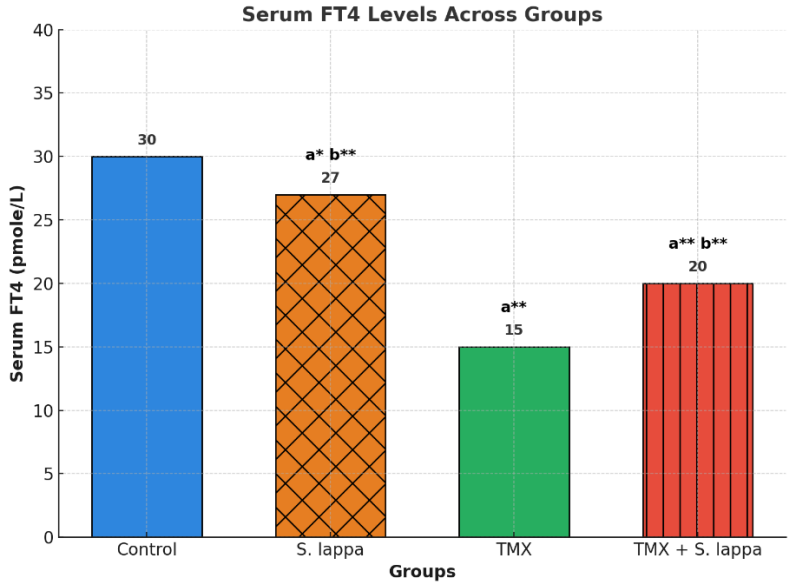

Figure3. Effect of *S lappa* root extract (SLRE) on serum FT4 levels in tamoxifen (TMX)-induced hypothyroidism in rats, $^{a**}P$=0.001, $^{a*}P$< 0.0 5 compared to control, $^{b**}P$= 0.001 compared to TMX.

Histomorphological Analysis of Thyroid Tissue

As shown in **Figures 4** and **5**, histological examination of thyroid gland sections from control rats and rats treated with SLRE alone revealed normal thyroid tissue architecture, characterized by well-defined spherical follicles. These follicles were lined by cuboidal epithelial cells containing spherical hyperchromatic nuclei. The follicular lumina were filled with eosinophilic gelatinous colloid (thyroglobulin) and were separated by connective tissue septa. Parafollicular cells (C-cells, calcitonin-secreting cells) were observed in clusters interspersed between the follicles. Thyroid follicular epithelial cells were actively involved in the production and reabsorption of colloid, visible as non-staining vacuoles, termed resorption lacunae, associated with the luminal membrane of the epithelial cells.

Histological sections from rats treated with TMX exhibited marked histopathological alterations, including shrinkage of the majority of thyroid follicles, degeneration of others with reduced colloidal areas, degeneration of follicular epithelial cells in some follicles, and rupture of the follicular sac in others. Additionally, thickening of the connective tissue between follicles was evident (**Figure 6**).

Conversely, thyroid sections from rats co-treated with TMX and SLRE displayed an apparently normal thyroid architecture with well-preserved follicles (**Figure 7**).

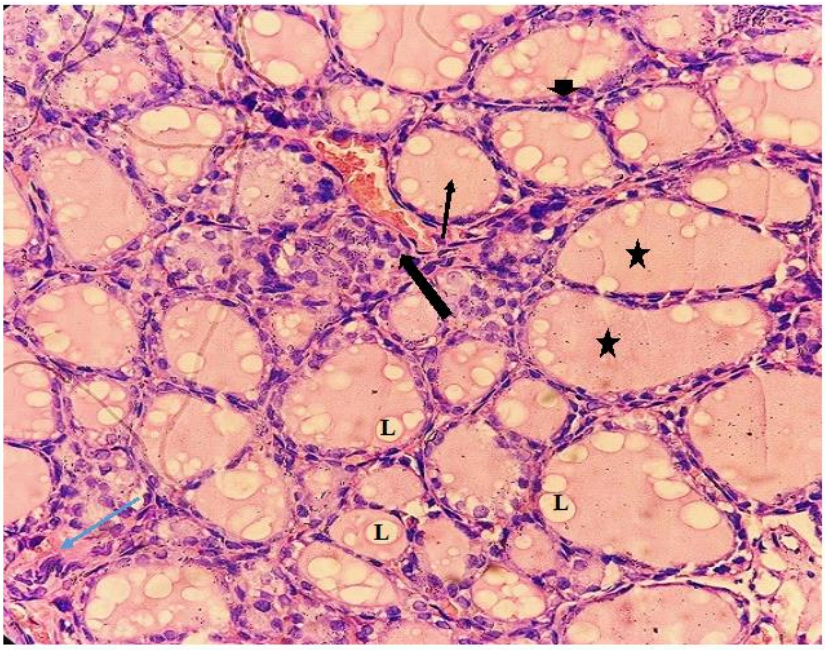

Figure4. Photomicrograph of a thyroid gland section from the control group of female rats, showing well-defined spherical follicles (thin arrow) lined by cuboidal follicular epithelial cells with spherical, hyperchromatic nuclei (arrowhead). The follicles are filled with an eosinophilic, gelatinous colloid (thyroglobulin) (asterisk) and exhibit resorption lacunae (L). The follicles are separated by connective tissue septa (blue arrow), and clusters of parafollicular cells (C-cells) are observed between the follicles (thick arrow). (H&E, ×400).

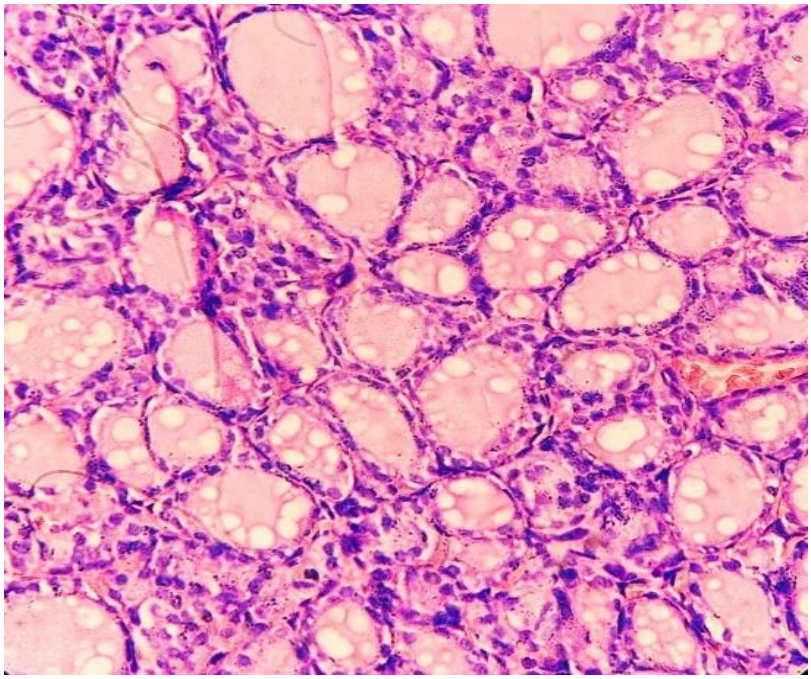

Figure5. Photomicrograph of a thyroid gland section from rats treated with *Saussurea lappa* root extract (SLRE), showing preserved thyroid architecture with well-organized follicles and intact cuboidal follicular epithelial cells (H&E, ×400).

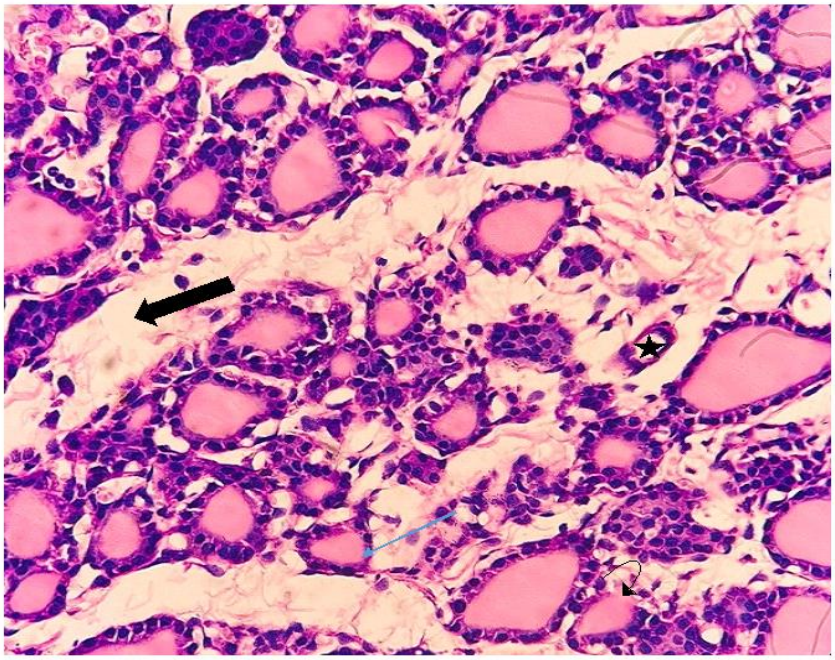

Figure6. Photomicrograph of thyroid gland section from rats treated with TMX showing disorganization of thyroid gland architecture with many histopathological changes, include shrinkage of most thyroid follicles and degeneration of others with a reduction of colloidal area (asterisk), degeneration of follicular epithelial cells (blue thin arrow) of some follicles and rupture of follicular sac of others (curved arrow) and thickening of connective tissue between follicles (thick arrow) (H&E X400).

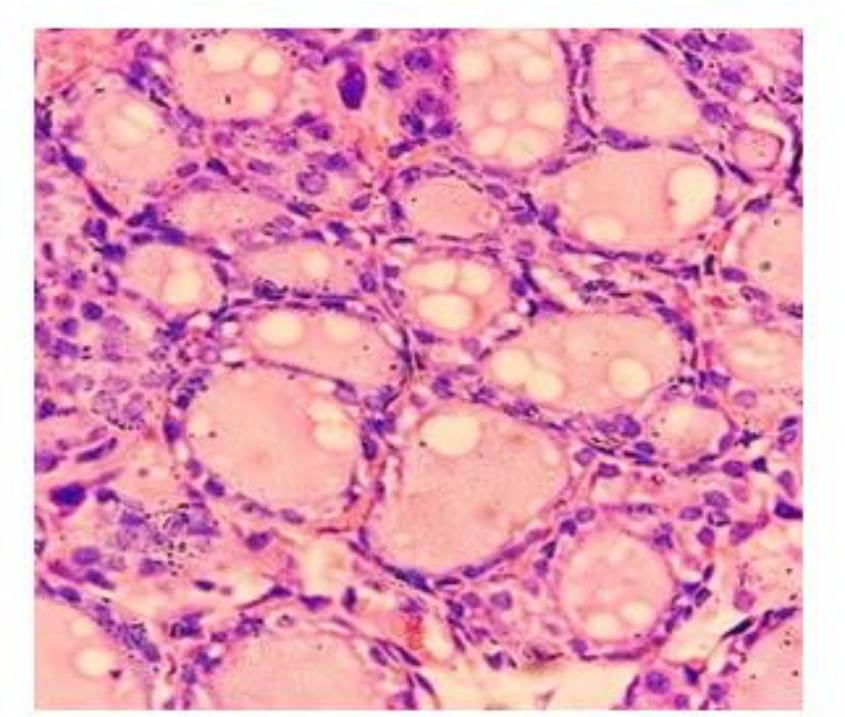

Figure7 . Photomicrograph of a thyroid gland section from rats treated concurrently with TMX and SLRE showing normal thyroid tissue architecture with well-preserved follicles (H&E, ×400).

Discussion

Tamoxifen, a selective estrogen receptor modulator, is widely utilized in the treatment of estrogen receptor-positive breast cancer (Furr & Jordan, 1984) However; evidence from various clinical studies suggests that TMX can influence additional endocrine pathways, notably the pituitary–thyroid axis (Grani et al., 2012; Athanassiou et al., 1998). This axis represents a vital neuroendocrine system responsible for regulating the synthesis and release of thyroid hormones. Disruptions in this system may result in thyroid dysfunctions such as hypothyroidism or hyperthyroidism (Rasmussen et al., 2021). Given this concern, the search for agents that can prevent or mitigate TMX-induced alterations in thyroid hormone levels has become a pressing need in the clinical management of breast cancer patients. Although herbal medicines are gaining popularity due to their cost-effectiveness and favorable safety profiles, scientific investigations addressing their potential in managing thyroid disorders remain relatively limited (Winterhoff et al., 1983; Panda & Kar, 1998).In this context, the present study was designed to evaluate the protective effect of the aqueous root extract of *Saussurea lappa* (AESL) against TMX-induced thyroid hormone disturbances in female rats.

The data of the current work revealed that administration of TMX induced disorder in thyroid function tests indicated by elevation of TSH in serum of TMX intoxicated rats in comparison to control animals. The increase in TSH was concomitant with depletion in serum FT3 and FT4. The present finding may suggest that TMX affect pituitary - thyroid gland system causing hormonal disorder. Similarly clinical study showed a significant increase in TSH at months 2–12 after TMX treatment (Athanassiou et al., 1998). Grani et al. (2012) reported that, among breast cancer patients undergoing tamoxifen therapy, 8.9% developed hypothyroidism and 4.4% developed hyperthyroidism after five years of treatment **(Grani et al., 2012).** The

deleterious effects of TMX were further confirmed histopathologically, as evidenced by severe disorganization of the histo-morphological architecture of the thyroid gland. These alterations included shrinkage of most thyroid follicles, degeneration of others with reduced colloidal area, degeneration of follicular epithelial cells in some follicles, and rupture of follicular sacs in others. Thickening of the connective tissue between follicles was also observed compared to controls. These histopathological changes in the thyroid gland of TMX-treated rats may, in part, explain the observed thyroid dysfunction. Several studies have investigated the mechanistic effects of tamoxifen (TMX) on the thyroid gland. Some researchers have reported that the presence of estrogen receptors in the thyroid indicates a direct influence of estrogens and estrogenic-stimulating agents on the gland (Chaudhuri et al., 1986). Additionally, it has been suggested that TMX may affect the thyroid indirectly by acting on the pituitary gland, thereby modulating the release of thyroid-stimulating hormone (TSH) (D'Angelo, 1968). Other investigations indicated that TMX interferes with the synthesis of total thyroxine (TT4), resulting in decreased bioavailability of both TT4 and triiodothyronine (TT3) (Anker et al., 1998). Beyssen et al. (2000) demonstrated that TMX can sequester iodine through the formation of charge-transfer complexes, which disrupt thyroid metabolism by reducing the availability of iodine within the gland, thus promoting hypothyroidism (Beyssen et al., 2000). Moreover, TMX exhibits antithyroid activity by inhibiting thyroid peroxidase, a critical enzyme involved in the biosynthesis of thyroid hormones T3 and T4 (Davies et al., 1995).Thyroid peroxidase catalyzes the oxidation of iodide to molecular iodine, a crucial step in hormone synthesis, as well as the iodination of tyrosine residues on thyroglobulin, a protein essential for thyroid hormone production (Davies et al., 1995). Hypothyroid rats induced by TMX and treated with SLRE exhibited significant improvement in thyroid function markers, including TSH, FT3, and FT4. In the hypothyroid + extract group, serum FT3 and FT4 levels increased by approximately 1.3-fold and 1.45-fold, respectively, while plasma TSH levels decreased by 1.34-fold compared to the hypothyroid group. These findings suggest that SLRE possesses therapeutic potential to restore thyroid hormone balance in experimentally induced hypothyroidism. The plant extract also restored the histology of the thyroid to a normal appearance. These observations are consistent with previous studies reporting that administration of *S. costus* extract ameliorates biochemical abnormalities associated with experimentally induced hypothyroidism (Bolkiny et al., 2019), with suggestions that *S. costus* roots may serve as an effective adjunctive therapy alongside thyroxine treatment (Bolkiny et al., 2019). Moreover, other studies have demonstrated the protective effects of Costus root extract against valproate sodium- and carbimazole-induced reductions in serum T3 and T4, as well as increases in TSH levels in rodent models (Mahmoud, 2020; Fekry et al., 2023). Clinically, *S. costus* is recognized for its relevance in treating thyroid disorders and maintaining thyroid hormone homeostasis within tissues (Mujammami, 2020). The beneficial modulatory effect of SLRE on thyroid hormones is likely attributed to its phytochemical constituents, particularly dehydrocostus lactone and costunolide, which have been shown to regulate cellular redox balance and inhibit inflammatory mediators, thereby protecting endocrine organs from oxidative stress and drug-induced toxicity (Saleem et al., 2013).

Conclusion

The present results demonstrated that TMX administration induced hypothyroidism in rats, as evidenced by decreased serum levels of FT3 and FT4, accompanied by a corresponding increase in TSH concentration. TMX treatment also caused disorganization of the thyroid histological architecture. Administration of SLRE to hypothyroid rats significantly ameliorated

these hormonal imbalances and restored the normal histological structure of the thyroid gland. These findings indicate that SLRE may serve as a potential adjunct therapy alongside TMX to mitigate or prevent TMX-induced thyroid dysfunction.

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