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Preservation Of Chemotherapy - Affected Thyroid Gland By Herbal Products- Iodine Rich Fraction

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Abstart:

This study was designed to investigate the protective effect of flaxseed and *fucus vesiculosus* against toxic effect of Doxorubicin o thyroid gland of male rats. Used in this study (48) male Swiss Albino rats were equally divided into eight groups. Group1 (negative control), treated with normal saline (N.S) intraperitoneal (IP) injection, group 2 (positive control), treated with 15 mg/kg Doxorubicin as a single (i.p) injection, group3 (third control), received 1.8ml/kg of the flaxseed oil orally, once daily for 4 weeks,group4 (four control), orally tread with fucus vesiculosus (50)mg/kg day for 30 day, group5 (five control), received of the flaxseed oil and fucus vesiculosus together orally, group6 (first treament),treated with Dox and then received flaxseed oil, group7 (second treatment), treated with Dox and then received fucus vesiculosus, group8 (third treatment), treated with Dox and then received flaxseed oil and fucus vesiculosus, and after the end experiment period and we extracted the organs we want study (thyroid gland). Histological examination of thyroid gland sections for different treated groups showed considerable changes as compared with non-treated as a positive control group, Thyroid follicles became larger, containing dense colloidal, with the presence of many profollicular cells in treatment of first, second and third groups, structures of thyroid follicles and moderate colloid material within follicles. It may be concluding that flaxseed oil and fucus vesiculosus have a role in inhibition of the toxic effect of chemotherapy, doxorubicin.

Key words: Doxorubicin, flaxseed oil, focus vesiculosus, thyroid gland.

1. Introduction:

Doxorubicin (DOX) (also called adriamycin) is a potent anthracycline antibiotic which have been widely used in the chemotherapy to treat a wide variety of malignancies (Sauter *et al*., 2010; Shi *et al*., 2011). In metastatic thyroid carcinoma, DOX is the best available agent, also it is an important ingredient for the successful therapy of Hodgkin's disease and non-Hodgkin's lymphomas and many other cancers (Kufe *et al*., 2003; Smith *et al*., 2010).

The exact mechanism of action of DOX as anticancer agent is not explained that, it has been attributed to the intercalation into DNA, leading to inhibition of macromolecular synthesis, preventing the replication of rapidly growing cancer cells (Sauter *et al*., 2010; Shi *et al*., 2011; Hynek *et al*., 2012).

The optimal use of doxorubicin is limited by a number of side-effects, the most important are cardiotoxicity, haematotoxicity (Al-Harbi *et al.*,1992) and a dose limiting nephrotoxicity (Jovanovic, *et al.*,1996).

DOX cytotoxicity and genotoxicity may be mediated by free radicals derived from this drug and its capability to induce apoptosis through a wide variety of mechanisms, including production of ROS, alkylation of cellular macromolecules, DNA intercalation and cross-linking, lipid peroxidation, cell membrane damage, ceramide production and p53 induction in various tissues (Bose *et al.,* 1995*;* Quiles *et al.,* 2002*;* Sparreboom, *et al*., 2002*;* Ashikawa *et al*., 2004).

This type of treatment has been demonstrated to be deleterious for the thyroid's integrity, resulting in thyroid dysfunction and degeneration (Tamura *et al*., 1981; Smith *et al*., 1981; Tell *et al*., 1997), which has implications for almost all other tissues (Atahan *et al*., 1998), especially during growth and development It is still an issue of debate whether chemotherapy has an additional detrimental effect on the thyroid gland.

Herbal drug therapy is considered a common practice adopted in traditional and alternative medicine and has been used in the treatment of many diseases from ancient times (Nabavizadeh, 2009). Plant material in the human diet contains a large number of natural compounds, which may be of benefit in protecting the body. Scavenging of free radicals, elevation of cellular antioxidants, induction of bone marrow recovery and extrahaematological tissue regeneration by plants and herbs in damaged systems could be leading mechanisms of protection (Joshi *et al*., 2010). One of the plants with constituents reputed to possess antioxidant properties was *Linum usitatissimum* and *Fucus vesiculosus*.

Linum usitatissimum (Flax seeds), also known as Linseeds, are commonly used as a source of protein supplements in the rations of dairy animals? According to (Petit *et al*., 2001), feeding on Flax seeds to dairy cows increased the first service conception rates by17%. Flax seeds also show many health benefits (Khan *et al*., 2010). Flax seeds have been shown to have antioxidant property (Rhee and Brunt, 2011) and prevent diabetic complications (Makni *et al*., 2011), while Lignan concentrate extracted from flax seeds showed cardioprotective effects in rats (Zanwar *et al*., 2011). Chemically, these seeds contain 41% oil, 20% protein and 28% dietary fiber and They are rich in essential omega-3 fatty acid and polyunsaturated linolenic acid (Conners, 2000). Flax seed oil has an effect on thyroid tissues (Idis *et al*., 2014).

Fucus vesiculosus (also known by the common name bladder wrack) is a marine alga rich in iodine, which is being used in alternative medicine as a laxative, diuretic, as a complement (for weight loss and as source of iodine), treatment of thyroid disorders, particularly hypothyroidism, rheumatoid arthritis and for its topical effects as a dermatological agent (Arbaizar and Llorca, 2011). It is rich in polysaccharides and polyphenolic antioxidants (phlorotannins) (Díaz-Rubio *et al*., 2009).

Aim of the study: -

In view of these considerations the objective of this work is to evaluate the use of Fucus vesiculosus and flaxseed oil to restoration of damged histological architectures components of thyroid tissue. As well as estimation of thyroid function via measuring dimention thyrotical follicales and thyrocytes heights.

2. Materials and Methods: -

a) Animals: -

Forty-eight male Swiss Albino rat (weighting 222 - 230 g) were used in our study. The rats were put in the animal house in the college of Education Pure Sciences in Thi - Qar university under constant conditions of temperature (22 ± 25) ºC and lighting (12:12hr light: dark cycle) for two weeks before and through the experimental work, the rat being maintained on a standard commercial rat and tap water is available *ad-libitum*.

b) Preparation of Plant: -

The plant herbs (capsules of *Fucus vesiculosus* and flaxseed oil) were provided prepared by Amazon American.

c) Experimental design:

The animals were randomly divided into 8 groups (6 rat in each group) as follows:

Group1: - (negative control): received normal saline (N.S) intraperitoneal (IP) injection for 30 days.

Group2: - (positive control): injected intraperitoneally (i.p) with 15mg/kg DOX (EBEWE Pharma Ges.m.b.H. Nfg.KG, AUSTRIA) (Nilesh Shinde *et al.*, 2010).

Group3: - (third control): Drenched 1.8ml/kg of flaxseed oil orally (p.o), once daily for 4 weeks.

Group4: - (fourth control), orally tread with focus vesiculosus (50) mg/kg day for 30 days.

Group5: - (fifith control), received of the flaxseed oil and focus vesiculosus together orally for 30 days.

Group6: - (first treament), treated with Dox and then received flaxseed oil for 30 days.

Group7: - (second treatment), treated with Dox and then received focus vesiculosus for 30 days.

Grop8: - (third treatment), treated with Dox and then received flaxseed oil and focus vesiculosus for 30 days.

At the end of the experiment, animal of each group were anesthetized by chloroform and sacrificed, thyroid of all groups were removed and kept in 10% formaline for histopathological study.

d) Histopathological study: -

Thyroid samples were dissected and fixed in formaline, dehydrated and imbedded in paraffin wax. The, the section were stained by haematoxylin and eosin (H&E) stain. Each slides was examined for histopathological changes under light microscope, based on (Bancroft and Gamble, 2008) , the diameters were then measured using an ocular micrometer.

e) Statistical Analysis: -

The results of the present study were analyzed by using one-way covariance (ANOVA) test in all study. All statistical calculations were carried out by the aid of the statistical package SPSS V. 17 (SPSS Inc.). The data were expressed as means± standard error (Mean ± SE). (Inc,2006).

3.Results: -

3.1 Statistical study: -

A. Effect of Doxorubicin and medicinal herbs in large follicles: -

❖ **Height of the epithelial tissue of the follicle: -**

The results showed an insignificant increase (P≤0. 05) in the positive control group (Dox-treated rats) compared with the first, second and third treatment groups (Dox-exposed rats treated flaxseed oil, Dox- exposed rats treated *Fucus vesiculosus* and Dox-exposed rats treated with combine flaxseed oil and *Fucus vesiculosus*) respectively mentioned in table (1).

❖ **Width of the follicle: -**

The current study showed a significant decrease (P≤0. 05) in the positive control group (Dox-treated rats) compared with the first, second and third treatment groups (Dox-exposed rats treated flaxseed oil, Dox- exposed rats treated *Fucus vesiculosus* and Dox-exposed rats treated with combine flaxseed oil and *Fucus vesiculosus*) respectively mentioned in table (1).

❖ **Length of the follicle: -**

The current study showed a significant decrease (P≤0. 05) in the positive control group (Dox-treated rats) compared with the first, second and third treatment groups (Dox-exposed rats treated flaxseed oil, Dox- exposed rats treated Fucus vesiculosus and Dox-exposed rats treated with combine flaxseed oil and Fucus vesiculosus) respectively mentioned in table (1).

Table (1): - Effect of Doxorubicin and medicinal herbs in large follicles of the thyroid tissue **(**mean ± stander error**)**

Adjective / Groups	Height of epithelium	Length	width
Group negative control	15.67♦ ± 1.02	149.33 ♦ ± 1.71	116.67 ♦ ± 5.64
Positive control	10 ♦❋ ± 0.00	75 ♦❋ ± 2.58	68 ♦❋ ± 4.82
Third control	17.33 ♦❋★ ± 0.67	141.67 ❋★ ± 0.84	149 ♦❋★ ± 3.20
Fourth control	14.67 ❋★ ± 1.28	96.67 ♦ ❋★ ± 1.58	120 ❋★ ± 2.58
Fifth control	9.83 ♦★ ± 0.11	128.33♦❋ ★ ± 5.45	154.33♦❋ ± 14.95
First treament	8.87♦ ± 0.16	113♦❋♦ ± 2.59	88.33♦❋ ± 3.68
Second treament	9.33♦ ±0.17	145❋♦ ± 7.77	88.33♦❋ ± 1.05
Third treament	9.83♦ ± 0.10	135♦❋♦ ± 2.88	83.33♦ ± 1.74
L.S. D	2.67	13.33	20.33

- ♦ There were significant differences between negative control group and other groups, At the probability level (P≤0.05).
- ❋ Significant differences between the positive control group and the other groups.
- ♦ Significant differences between the three treatment groups.
- ★ Significant differences between the third, fourth and fifth control groups.

B. Effect of Doxorubicin and Medicinal Herbs in the Mid-follicle:

❖ **Height of the epithelial tissue of the follicle: -**

The results of the statistical analysis of the current study showed a significant increase (P≤0.05) in the positive control group compared to the first, second and third treatment groups,shown in Table (2).

❖ **Width of the follicle: -**

The results of the current study showed a significant decrease (P≤0.05) in the positive control group compared with the groups (the second and third treatments), and insignificant decrease in the positive control group compared to the first treatment group at the mentioned probability level, As in the table (2).

❖ **Length of the follicle: -**

The results showed a significant decrease(P≤0.05) in the positive control group compared to the first, second and third treatment groups, shown in Table (2).

Table (2): - Effect of Doxorubicin and medicinal herbs in Mid- follicles of the thyroid tissue (mean ± stander error)

Adjective / Groups	Height of epithelium	Length	width
Group negative control	9.67 ♦ ± 0.21	112.33 ♦ ± 3.37	93 ♦ ± 3.57
Positive control	9.50 ❋ ± 0.26	70 ♦ ❋ ± 3.02	56 ♦❋ ± 1.52
Third control	9 ± 0.43	82.67♦ ❋ ★ ± 6.29	71.67 ♦❋★ ± 7.29
Fourth control	8.33❋★ ± 0.60	116.67❋ ★ ± 4.21	118.33♦❋★ ± 2.84
Fifth control	9.60★ ± 0.14	90 ♦❋★ ± 4.75	103.33♦❋★ ± 1.99
First treament	8.77♦ ± 0.12	89.33♦❋♦ ± 1.94	58.33♦♦ ± 1.05
Second treament	8.40♦❋ ±0.10	111.67❋♦ ± 3.35	66.67♦❋♦ ± 1.71
Third treament	8♦❋ ± 0.14	111.67❋♦ ± 3.40	77.67♦❋♦ ± 1.12
L.S. D	0.90	12.67	10

- ♦ There were significant differences between negative control group and other groups, At the probability level (P≤0.05).
- ❋ Significant differences between the positive control group and the other groups.
- ♦ Significant differences between the three treatment groups.
- ★ Significant differences between the third, fourth and fifth control groups.

C. Effect of Doxorubicin and medicinal herbs in Small follicles: -

❖ **Height of the epithelial tissue of the follicle: -**

The current study showed a significant decrease (P≤0.05) in the positive control group compared to the to the first, second and third treatment groups,shown in Table (3).

❖ **Width of the follicle: -**

The results showed a significant decrease (P≤0.05) in the positive control group compared to the second and third treatment groups and insignificant decrease in the positive control group compared with the first treatment group at the mentioned probability level, As in the table (3).

❖ **Length of the follicle: -**

The results of the statistical analysis showed a significant decrease (P≤0.05) in the positive control group compared to the first, second and third treatment groups, As in the table (3).

Table (3): - Effect of Doxorubicin and medicinal herbs in Small follicles of the thyroid tissue (mean ± stander error)

Adjective / Groups	Height of epithelium	Length	width
Group negative control	8♦ ± 0.00	53.33 ± 0.	53 ± 1.93
Positive control	8.40 ❋ ± 0.34	50.67 ± 1.52	43.33 ± 1.49
Third control	5.60 ♦❋★ ± 0.32	49.33 ± 1.43	50.33 ± 0.76
Fourth control	7.33 ★ ± 0.84	61.17 ± 0.84	56.67 ± 1.96
Fifth control	8.50 ★ ± 0.72	40 ± 2.63	63.33 ± 1.54
First treament	6.93❋♦ ± 0.10	63.33 ± 1.05	46.67 ± 1.96
Second treament	6.50♦❋♦ ± 0.37	88.33 ± 3.99	55 ± 1.50
Third treament	4.50♦❋♦ ± 0.18	69.33 ± 3.23	48.33 ± 0.84
L.S. D	1.5	7.67	4.67

- ♦ There were significant differences between negative control group and other groups, At the probability level (P≤0.05).
- ❋ Significant differences between the positive control group and the other groups.

- ♦ Significant differences between the three treatment groups.
- ★ Significant differences between the third, fourth and fifth control groups.

3-2 Histological study: -

The histological study of the thyroid gland in male laboratory rats showed that the thyroid tissue was normal. The follicles lining a layer of epithelial cells containing the nucleus can be seen as large, followed by medium and then small. A colloid is perfectly homogeneous and squamous cells are normal as in Fig. (1a) and (1b). The histological study in male laboratory rats showed positive tissue changes compared with the negative control. The presence of hyperplasia was evident in the thyroid tissue, where the follicular cells appear to proliferate. We also notice in the adjacent follicales degeneration with degeneration with Necrosis of the cells lining the follicles as well as the small size of the follicles, also noted the loss of tissue for some of its precise features, as well as a small rise in the cells epithelial epithelial cells cubic and vertical for follicles as in figure (2a) and (2b). The results of the microscopic examination in the fourth control group did not show any type of tissue deformities. The tissue showed a good response to the extract, which resulted in the growth of various follicles, especially the recently formed colloid and the mature follicles containing the gluten, which confirms the natural effectiveness. The thyroid gland was characterized by the presence of cell follicular. The septum of the gland separated by the connective tissue septa and the blood vessel between the connective tissue and the parathyroid glands, which were identified by cells The main cells and the acid cells Oxphil cells compared to the control group that looked normal as in fig (7a) and (7b).

The results of the histological examination in the third control group showed that the thyroid tissue showed improvement as the thyroid follicles were clear and normal and filled with homogenous glaucoma.Fig.(6a and 6b) the thyroid gland was identified.

The results of the histological examination in the fifth control group improved by the growth of many follicles of different sizes, especially the structural ones, which are missing to the granule and mature follicles containing the collagen, which confirms the natural effectiveness. As in the fig. (8a) and (8b).

The results of the histological examination of the current study showed an improvement in the tissue sections of the treatment of first, second and third groups, showed activation of the thyroid gland in all three groups treated as the thyroid follicles are larger, and denser of the granule, as can be noted tissue link between thyroid follicles and rich in blood vessels. The presence of many modern cells composition and the ideal installation of thyroid follicles with moderate amounts of granular inside the follicles as in the forms (3a), (3b), (4a), (4b), (5a) and (5b).

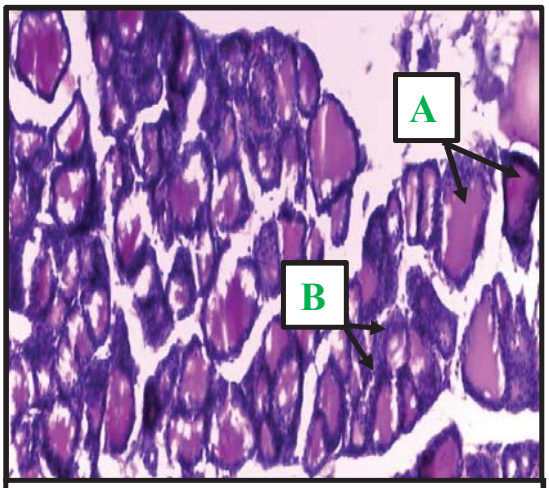


Figure (1a): - A transverse section of the thyroid gland of the negative control group shows: A follicle filled with colloid B-cells of the epithelial tissue are normal. (100X H & E).

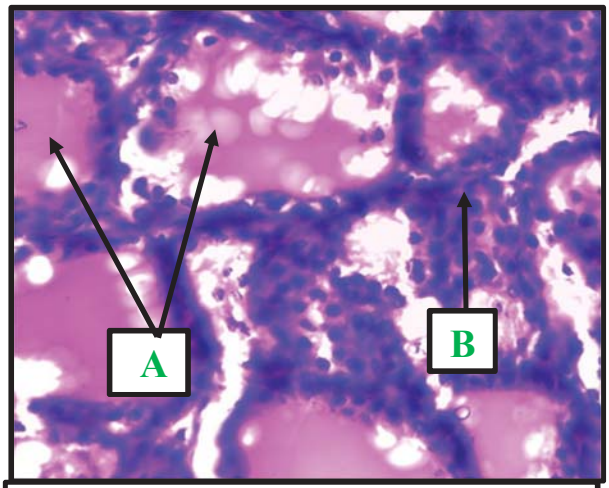


Figure (1b): - A transverse section of the thyroid gland of the negative control group shows: A follicle filled with colloid B-cells of the epithelial tissue is normal. (400X H & E).

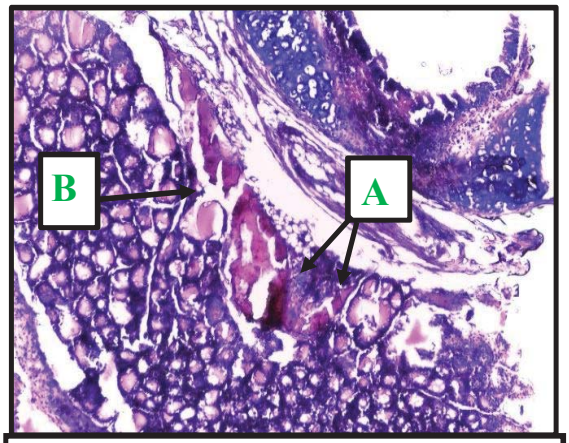


Figure (2a): - A transverse section of the thyroid gland of the positive control group shows: A-area of hyperplasia is clearly proliferating B- follicular cells are proliferated by papillary projections. (100X H & E).

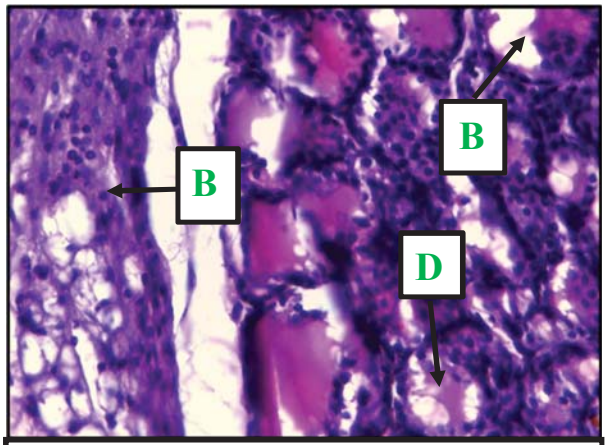


Figure (2b): - A transverse section of the thyroid gland of the positive control group shows: A-area of hyperplasia is clearly proliferating B- disappearance and disappearance of chromosome D- degeneration clear with necrosis of follicular cells. (400X H & E).

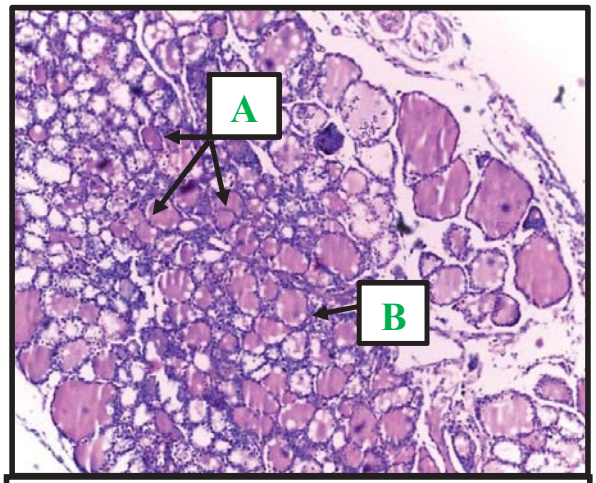


Figure (3a): - A cross section of the thyroid gland of the group shows the first treatment: a - small follicles in large numbers showing complete heroin B. Clear clone of the cells of the follicle (100x H & E).

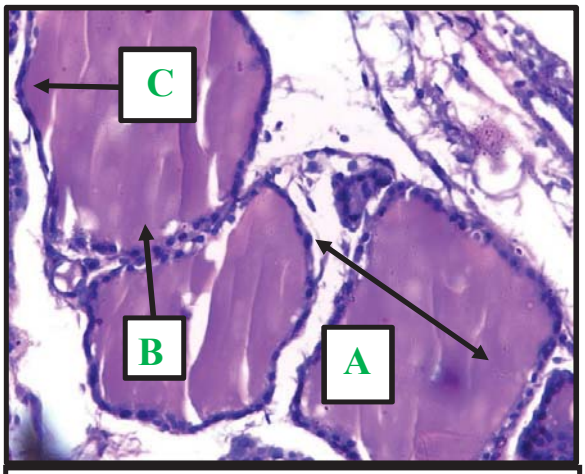


Figure (3b): - A- transverse section of the thyroid gland The first treatment shows: A- The size of the follicles B- The epithelial cell height of the follicles C- Colloid homogeneity (400X H & E).

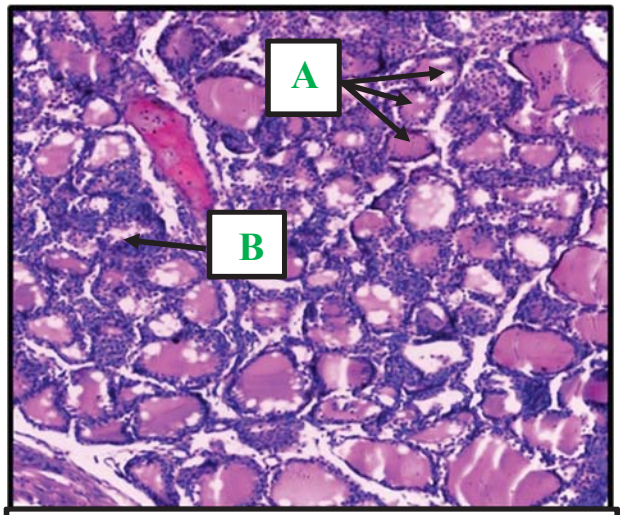


Figure (4a): - A transverse section of the thyroid gland of the second treatment group A - the presence of small follicles in large numbers appear full of colloid B - a clear proliferation of cells lining the follicles (100X H & E).

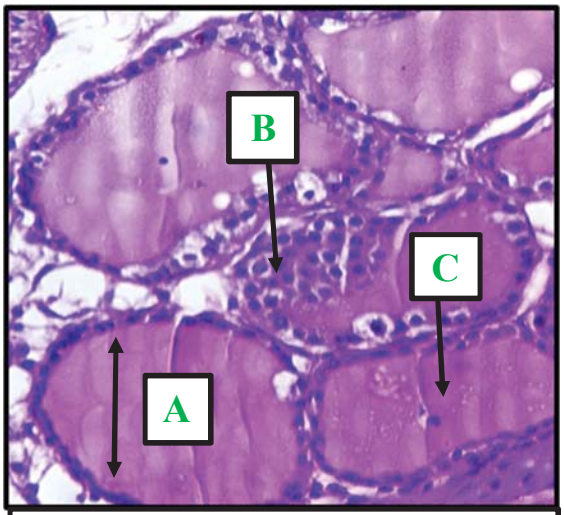


Figure (4b): - A transverse section of the thyroid gland of the second treatment group: A - size of scabies B - height of epithelial cells of the follicles C - homogenous colloidal (400X H & E).

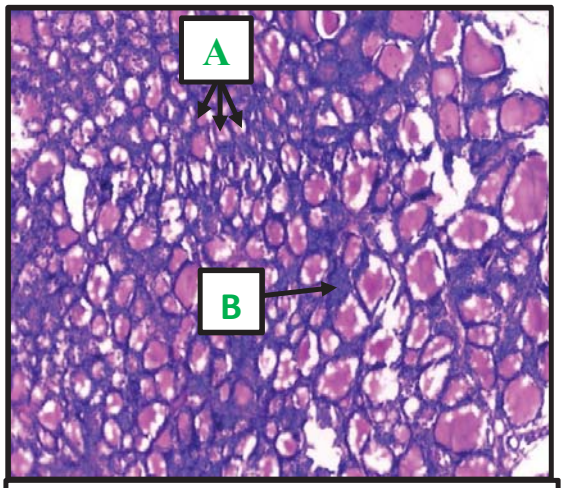


Figure (5a): - A transverse section of the thyroid gland of the group The third treatment shows: A- Small follicles in large numbers showing full of colloid B. Clear reproduction of follicular cells (100X H & E).

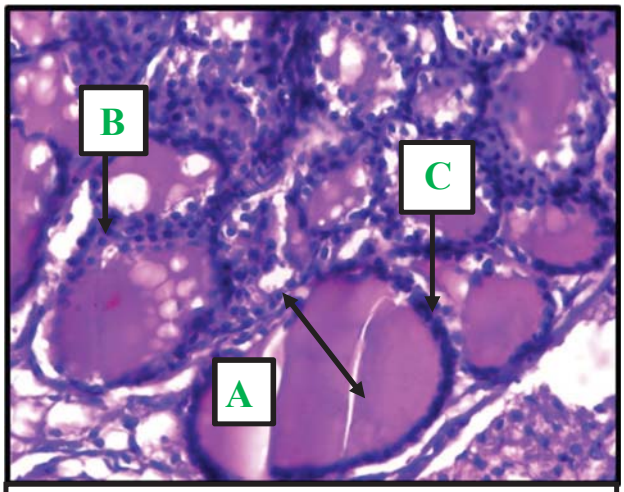


Figure (5b): - Transverse section of the thyroid gland of the third treatment group: A - size of the scabies B - the rise of epithelial cells of the follicles C - homogenous colloidal cell (400X H & E).

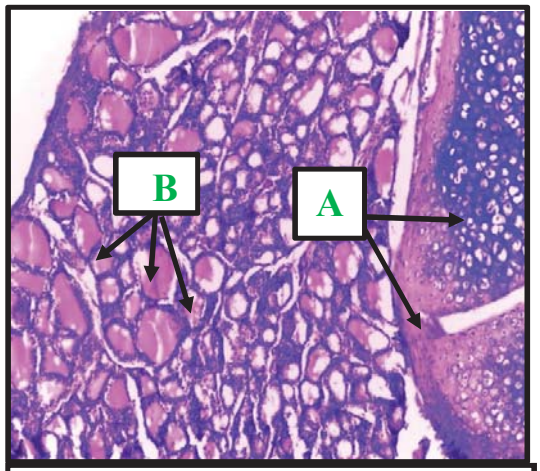


Fig. (6a): - A transverse section of the thyroid gland of the third control group showing: A - the presence of normal follicles in large numbers appear full of colloid B - Diagnosis of the parathyroid gland (100X H & E).

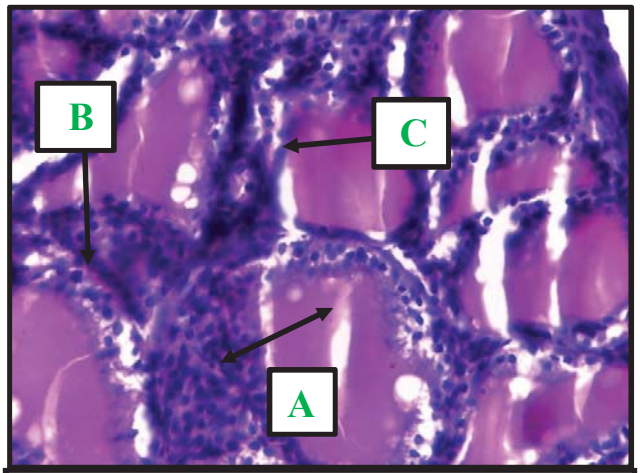
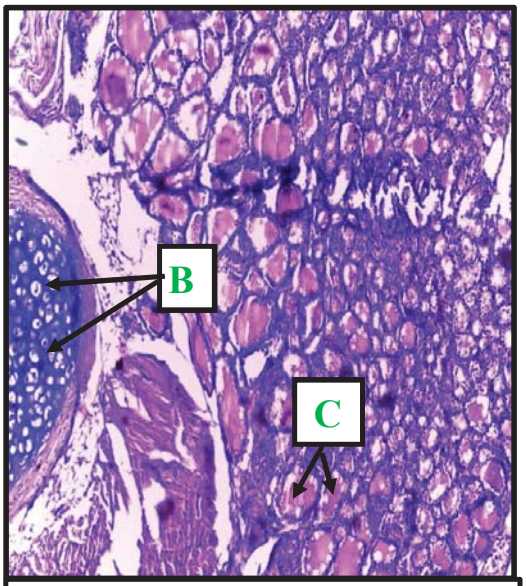


Fig. (6b): - A transverse section of the thyroid gland of the third control group showing: A - size of scabies B - rise of epithelial cells of follicles C - homogenous colloidal (400X H & E).



Fifure (7a): - A transverse section of the thyroid gland of the fourth control group shows: A-follicular cells and colloidal material B- Para-thyroid gland (primary and acidic cells) (100X H & E).

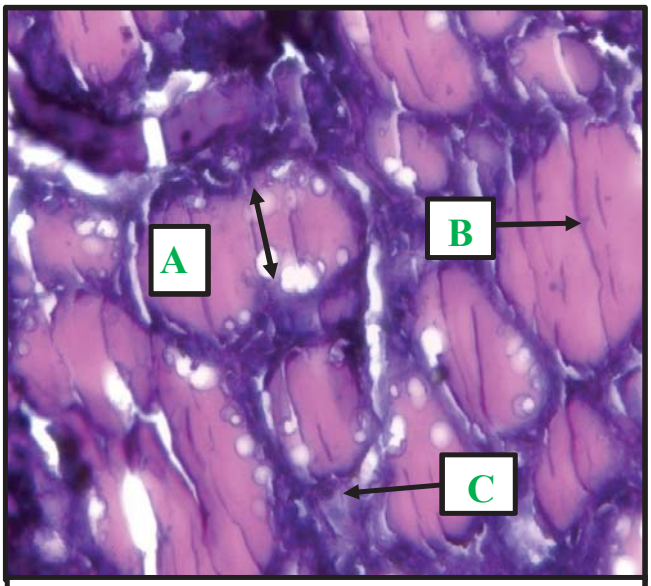


Figure (7b): - A transverse section of the thyroid gland of the fourth control group showing: A - size of scabies B - height of epithelial cells of follicles C - homogenous colloidal (400X H & E).

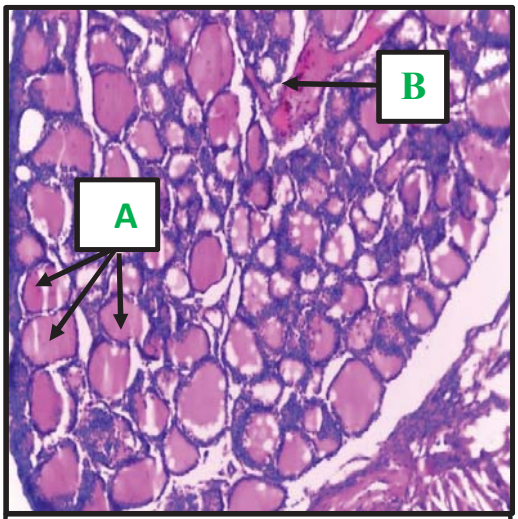


Fig. (8a): - A transverse section of the thyroid gland of the fifth control group shows: A - the presence of normal follicles appears full of colloid B - barriers between the lobes and blood vessels (100 X H & E)

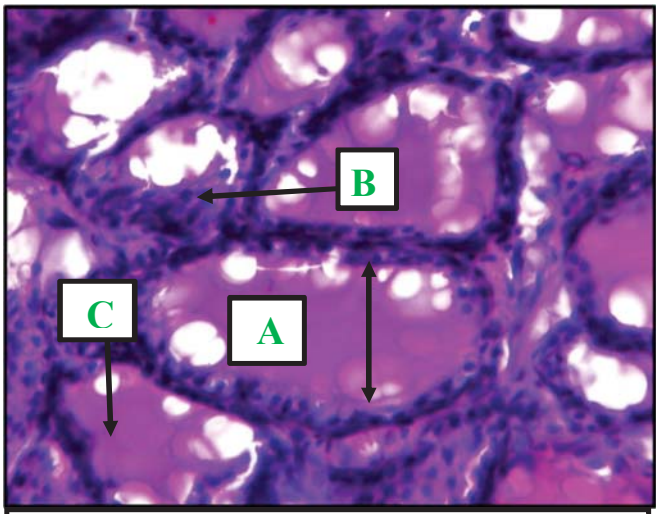


Fig. (8b): - A transverse section of the thyroid gland of the fifth control group shows: A - size of scabies B - height of epithelial cells of follicles C - homogeneous colloidal (400X H & E).

Discussion:

Microscopical examination of thyroid of (DOX) treated group reveal the marked damage to thyroid tissue,This damage may be result from the oxidative stress induced by doxorubicin. The free radicals generated by the oxidative stress act of the attack of the thyroid cells, causing damage in their membranes, leading to morphological changes in the thyroid gland such as necrosis and degeneration. Cancer survivors and recipients of chemotherapy for degeneration of thyroid tissue (Hancock *et al.*,1991). The study of histological sections showed the presence of hyperplasia and may be due to the reduction of thyroid hormone in the blood, which stimulates the secretion of TSH hormone from the pituitary gland and this leads to hyperthyroid hypertrophy and hyperthyroidism of thyroid gland without corresponding increase in the level of thyroid hormone in blood (Hood *et al*., 1999; Capen, 2004). Or this phenomenon usually occurs in some tissues as a result of adapting them with any physiological imbalance in the secretion of hormones (Kumar *et al*., 2003), which resulted from the administration of dexorubicin or the disappearance of the gluten due to the release of thyroid hormones and the survival of follicles free of gluten (Stevens and Lowe, 1997). Because of the degeneration and the damage caused?

The results of the statistical analysis and microscopic examination of the third control group histology showed an improvement in tissue sections. This is due to the fact that flaxseed contains lignan, which is a powerful antioxidant and is rich in omega-3 fatty acids and linolenic acid (Conners, 2000; Zanwar *et al*., 2011). This corresponds to a study (Wafaa *et al*., 2017) where improvement was observed in the histological sections of thyroid gland in laboratory rats treated with flaxseed.

The results of the statistical analysis and microscopic examination of tissue sections of the fourth control group showed an improvement in the thyroid tissue due to the *fucus vesiculosus* components that contain compounds that affect the response of the thyroid cells to TSH, including the increased activity of the gland, which stimulates the production of colloidal and follicular follicles (Eroschenko, 2008) , And some studies suggest that the appearance of low-density gullies and granules suggests that the activity of some enzymes such as Peroxidase and Deiodinase increases the effectiveness of the gland in iodine capture to manufacture hormones (Conti *et al*., 1978; Kumar and Hagler, 1996). This corresponds to the results of our current study, as the level of T_3 and TSH has decreased significantly with the rise in the level of T_4.

The results of the statistical analysis and the histological examination of the fifth control group showed that the treatment of flaxseed oil and *fucus vesiculosus* showed an evolutionary appearance in the histological sections due to the above mentioned reasons in the third control groups treated with flaxseed oil and the fourth treatment with vesicular vesicle.

The results of the statistical analysis and the microscopic examination of the sections of the first, second and third treatment groups revealed an improvement in the histological lesions in the groups when the *fucus vesiculosus* and flaxseed were given separately or together. *Fucus vesiculosus* (containing high concentrations of vitamin C) and flaxseed oil (containing Lignan, omega-3 fatty acids and linolenic acid) is a powerful source of energy, protecting the integrity of cell membranes and repairing DNA damage from free radical damage. Both fucus vesiculosus and flax seed oil activate many enzymes and metabolic processes. They activate the enzyme adenylcyclase and inhibit the phosphorysterase inhibitory enzyme (AMP). This increases the levels of adenosine cyclophosphate (CAMP). Metabolism in tissues requires this increase in C-AMP Weimize cells. This may be due to the fact that flaxseed oil and fucus vesiculosus are protective measures that reduce the toxic effect of doxorubicin and its use as an antioxidant to scavenge the free radicals generated by the oxidative stress responsible for the tissue breakdown as it works to stop free radicals and then lead to Improved tissue and maintained tissue cohesion (Ferrari, 2000; Khalaf *et al*.,

2002). It is involved in many biochemical processes in biogeochemical systems that stop the oxidation of fat in cell membranes (Gurer and Ercal, 2000; Kucuk *et al.*, 2003).

The group treated with (flaxseed oil and *fucus vesiculosus* together) significantly improved the tissues of the thyroid gland as the tissues and arrangement of close to the sections taken from the control group of negative, as well as the presence of epithelial cells in their natural form and the convergence of follicles in their sizes because the thyroid cells restore their natural effectiveness in secretion Hormones (Singh, 1997). This is due to the strength of the synergy between the studied antioxidants, which are ionic complex, which increases their strength as they increase the antioxidants, the body's defense systems remove the oxygen-free radicals that damage the tissues (Ann and Rafel, 2006). Falaxseed oil and *fucus vesiculosus* play an important role in protecting cell membranes from destruction by lipid peroxidation by providing internal oxidative antioxidants as well as repairing DNA and RNA damage, thereby minimizing deformities. *Fucus vesiculosus* action also reduces hypothyroidism and improved tissue to contain flavonoids that reduced oxidative stress and raised the level of antioxidants in the body and demonstrated by the results of the study (Elst *et al*., 1991).

References:

1. **Al-Harbi M, Al-Garably M, Al-Shabanah O, Al-Bekairi A, Osman A, Tawfik H (1992).** Cancer Chem Pharmacol; 31: 200-204.
2. **Anna Bzducha and Rafel Wolosiak. (2006)** Synergistic effect of antioxidant activityof casein and its enzymatic hydrolysate in composition with ascorbic acid and β-carotene in model oxidation system. Act Sci. Polo. Technol. Aliment .5(1), 113-133.
3. **Arbaizar, B and Llorca, J. (2011).** *Fucus vesiculosus* induced hyperthyroidism in a patient undergoing concomitant treatment with lithium Actas Esp Psiquiatr;39(6):401-3.
4. **Ashikawa K, Shishodia S, Fokt I, Priebe W, Aggarwal B B. (2004).** Evidence that activation of nuclear factor-κB is essential for the cytotoxic effects of doxorubicin and its analogues. Biochemical Pharmacology. 67(2): 353-364.
5. **Atahan IL, Yildiz F, Ozyar E, Uzal D, (1998**). Thyroid dysfunction in children receiving neck irradiation for Hodgkin's disease. Radiat Med 16:359–361**.**
6. **Bancroft, J, D. and Gamble, M. (2008)**. Theory and practices of histological technique. 2 and ed. Churchill Elseirier. London., Pp: 56.
7. **Bose R, Verheij M, Haimovitz-Friedman A, Scotto K, Fuks Z, Kolesnick R. (1995).** Ceramide synthase mediates daunorubicin-induced apoptosis: an alternative mechanism for generating death signals. Cell. 82: 405–414.
8. **Capen, C, (2004).** Pathophysiology of Thyroid Gland. In: Veterinarypathophysiology (1st ed). by: Dunlop, R. H. and Malbert, C.H.(eds.) Blak Well Publishing. USA.pp:67-44.
9. **Conners, W.E. (2000).** Importance of N-3 fatty acids in health and disease. *Amer J Clin Nutr*. 71: 171-175.
10. **Conners, W.E. (2000).** Importance of N-3 fatty acids in health and disease. Amer J Clin Nutr. 71: 171-175.
11. **Conti, A., Studer, H., Kenenbuehl, F. and Kohler (1978)**, H. Regulation of thyroidal deiodinase activity. Endocrind .1978: 102:321-329.
12. **Díaz-Rubio, M. E., Pérez-Jiménez, J. & Saura-Calixto, F. (2009).** Dietary fiber and antioxidant capacity in *Fucus vesiculosus* products. Int. J. Food Sci. Nutr. 60 Suppl. 2:23-34.

13. **Elst, J.; Heide, D and Kohrle, J, (1991).** In vivo effects of flavonoids EMD 21388 on thyroid secretion and metabolism. Am. J. Physiol. Endocrinol. Metabol. 261: E227-E232.
14. **Eroschenko, V. P (2008).** Atlas of histology with Functional Correlations. 11th ed. Lippincott Williams and Wilkins. USA.; PP.349,395,382.
15. **Eroschenko, V. P (2008).** Atlas of histology with Functional Correlations. 11th ed. Lippincott Williams and Wilkins. USA; PP.349,395,382.
16. **Ferrari, C. K. B. (2000).** Free radicals, Lipid peroxidation and antioxidants in apoptosis: Implication in cancer, cardiovascular and neurological diseases. Biol. Bratislava, 55 (6): 581 – 590.
17. **Gurer, H. and Ercal, N. (2000).** Can antioxidants be beneficial in the treatment of lead poisoning. Free-radical Biol. Med., 29 (10): 927– 945.
18. **Hancock S, Cox R, McDougall I (1991).** Thyroid disease after treatment of Hodgkin's disease. N Engl J Med; 325:599-605.
19. **Hancock S, Cox R, McDougall I (1991).** Thyroid disease after treatmentof Hodgkin's disease. N Engl J Med 1991; 325:599-605.
20. **Hood, Y. P. Liu, V. H. Gattone, and C. D. Klaassen**, **(1999)** "Sensitivity of thyroid gland growth to thyroid stimulatinghormone (TSH) in rats treated with antithyroid drugs," Toxicol Sci, vol. 49, no. 2, pp. 263–271.
21. **Hynek, D.; Krejcova, L.; Zitka, O.; Adam, V.; Trnkova, L. and Sochor, J. (2012).** Electrochemical Study of DOX Interaction with Different Sequences of Double Stranded Oligonucleotides, Part II, Int. J. Electrochem. Sci., 7: 34-49.
22. **Idiz,** Erhan, A.; Deniz, F.; Yeliz, E.E.; Merve, B.C.; Huseyin, A.; Arda, I. and Mahmut, M. **(2014).** Efficacy of glycerol and flax seed oil as anti-adhesive barriers after thyroidectomy, Med Sci Monit, 2014; 20: 1090-1094.
23. **Joshi, Y.M.; Jadhav, T.A.; Kadam, V.J. (2010).** A pharmacological intervention for protection against ionizing radiations: A review. The Internet Journal of Internal Medicine. 8 (2): 1-20.
24. **Jovanovic D, Djukanovic I, Susic D, Funduk G, Jovanovic Z, Dragojlovic Z, Boydanovic G, Starcevic Bonzovic Z (1996).** The effect of captopril on the development of adriamycin nephropathy in rats with spontaneous arterial hypertension Srp Arh Celok Lek; 124 (1): 47-49.
25. **Khalaf, B. H.; Numan, N. A. and Wohaieb, S. A. (2002).** The effect of the effect of vitamins C and E, and allopurinol on the antioxidant status in asthmatic patients. Iraqi. J. pharm., 2: 30- 39.
26. **Khan, M.; Sharif, L.; Sarwar, M.; Sameea, M. and Ameen, M. (2010).** Chemical composition of different varieties of linseed. *Pak Vet J*.30: 79-82.
27. **Kucuk, O.; Sahin, K.; Gursu, M. F.; Gulcu, F.; Ozcelik, M. and Lssi, M. (2003).** Egg production, egg quality, and lipid peroxidation status in laying hens maintained at alow ambient temperature (6C) and fed a vitamin C and E. supplemented diet. Vet. Med. Czech., 1 (2): 33- 40.
28. **Kufe, D.W.; Holland, J.F. and Frei E. (2003).** American Cancer Society: Cancer medicine 6., BC Decker, Hamilton.
29. **Kumar, V. and Hagler (1996).** H. Pathologic (Basis of Discase) .6th ed. W.B. Saunders Company, Philadephia.
30. **Kumar, V.; Cotran, R.; Robbins, S. (2003)**. Basic pathology.7th ed. W. B. Saunders Company. p: 8-55, lead poisoning. Free-radical Biol. Med., 29 (10): 927– 945.

31. **Makni, M.; Sefi, M.; Garoui, E.l. M.; Fetoui, H. Boudawara, T and Zeghal, N. (2011).** Dietary polyunsaturated fatty acid prevents hyperlipidemia and hepatic oxidant status in pregnant diabetic rats and their macrosomic offspring. *J Diabetes Complications*, 25: 267-274.
32. **Nabavizadeh, S, H.; Majid, O. and Anushiravani, A. (2009).** Direct ex vivo effects of herbal extracts on serum bilirubin in neonatal blood samples. African Journal of Biochemistry Research;3(5):226-228.
33. **Nilesh Shinde, Amit Jagtap, Vaishali Undale, Sujit Kakade, Sachin Kotwal, Ravindra Patil, (2010);** Protective effect of Lepidium sativum against doxorubicin-induced nephrotoxicity in rats, Research Journal of Pharmaceutical, Biological and Chemical Sciences Volume 1 Issue 3 Page No. 42-48.
34. **Petit, H.V.; Dewhurst, R.J.; Proulx, J.G.; Khalid, M.; Haresign, W. and Twagiramunugu, H. (2001).** Milk production, milk composition and reproductive function of dairy cows fed different fats. *Canadian J Anim Sci*, 81: 263-271.
35. **Quiles J, Huertas J, Battino M, Mataix J, Ramirez-Tortosa M. (2002).** Antioxidant nutrients and adriamycin toxicity. Toxicology.180, 79–95.
36. **Rhee, Y and Brunt, A. (2011).** Flaxseeds supplementation improved insulin resistance in obese glucose intolerant people: a randomized crossover design. *Nutr. J*. 10: 44.
37. **Sauter, K.A.D.; Magun, E.A.; Iordanov, M.S. and Magun, B.E. (2010).** ZAK is required for DOX, a novel ribotoxic stressor, to induce SAPK activation and apoptosis in HaCaT cells Cancer Biology & Therapy, 10 (3): 258-266.
38. **Shi, Y.; Moon, M.; Dawood, S.; McManus, B. and Liu, P. (2011).** Mechanisms and management of DOX cardiotoxicity. Herz, 36 (4): 296-305.
39. **Singh, I. (1997)**. Text book of human histology. 3rd ed. Jaypee Brothers. Medical Publishers LTD. p: 184-292.
40. **Smith Jr RE, Adler AR, Clark P, Brinck-Johnsen T, Tulloh ME, Colton T (1981).** Thyroid function after mantle irradiation in Hodgkin's disease JAMA 245. 46–49**.**
41. **Smith, L.A.; Cornelius, V.R.; Plummer, C.J.; Levitt,G.; Verrill, M.; Canney, P. and Jones, A. (2010):** Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer; 10:337.
42. **Sparreboom, A.; Nooter, K. and Verweij, J. (2002).** Mechanisms of Action of Antitumour Antibiotics. Rotterdam Cancer Institute, Netherlands. pp. 4.
43. **Sparreboom, A.; Nooter, K. and Verweij, J. (2002).** Mechanisms of Action of Antitumour Antibiotics. Rotterdam Cancer Institute, Netherlands. pp. 4.
44. **Stat Soft Inc., (2006).** Electronic statistics textbook. Tulsa, Oklahoma.
45. **Stevens, A. and Lowe, J. (1997).** Human histology. 2nd ed. Mosby. P: 123-261.
46. **Tamura K, Shimaoka K, Friedman M (1981).** Thyroid abnormalities associated with treatment of malignant lymphoma. Cancer 47:2704–2711.
47. **Tell R, Sjodin H, Lundell G, Lewin F, Lewensohn R (1997).** Hypothyroidism after external radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys Sep 1;39(2):303-8.
48. **Wafaa H. Haran Muna H. AL-Saeed Eman A. AL-Masoudi. (2017).** Study the effect of flax lignin extract of linum Usitatissimum and conjuga the wstrogen on physiological parameters in femalerats. College of Veterinary. Medicine, University of Basrah, p:20-49.