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MOLECULAR STUDY THE EFFECT OF FUCUS VESICULOSUS ON PITUITARY GLAND AND THYROID GLAND IN MALE RATS TREATED WITH PROPYLTHIOURACIL

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Abstract

The present study aims to identify the effects of the fucus vesiculosus on the TSH expression in the tissue of pituitary gland of mature male rats treated with Propylthiouracil (PTU). The sample is divided into five groups in addition to the control group. All groups are equal in number where each group includes ten rats. The control group has been given distilled water. The first treatment (T1): fucus vesiculosus of 35 mg/ kg concentration of body weight is given, (T2): propylthiouracil (PTU) of 15 mg/kg concentration of body weight is dosed, (T3): fucus vesiculosus of 35 mg/ kg concentration of body weight is given for three weeks then (PTU) of 15 mg/kg concentration is dosed for the other three weeks, (T4): propylthiouracil (PTU) of 15 mg/kg concentration of body weight is dosed for three weeks then fucus vesiculosus of 35 mg/ kg concentration of body weight is given for three weeks and in (T5) fucus vesiculosus and (PTU) are dosed together with the same concentration for 42 days.

In the end of the experiment, the animals are vivisected to exsect thyroid gland and pituitary gland for molecular study to estimate messenger ribonucleic acid (mRNA) of (TPO and TSH) genes using qRT-PCR qualitative technique. The results of molecular study show that there is an increase by (10.458) in the level of TSH in the pituitary gland tissues in T1 when compared with the control group (1.061). Also, there is a significant increase by (2.926) of gene expression in T3. In T4, the increase is (4.569) but TSH gene expression decreases in T2 while there is no significant difference in T5 by (1.269). As for TPO gene expression in thyroid tissues, there is a decrease in gene expression in T1 by (0.882) when compared with the control group by (1.056). There is a decrease in TPO gene expression in T2, T3 and T4, (8.198), (3.253) and (5.978) respectively. But there is an increase of gene expression in T5 by (1.704) when compared with the control group.

Introduction

Fucus vesiculosus is one of laminariales that belong to the family of seaweed. It has a long history of use as food and medication due to its biological properties. It is considered one of the natural antioxidant, which prevents free radicals (Song et al., 2000). It prevents tumours, motivates Lipase enzyme, minimizes cholesterol level, maintains blood sugar levels, activates and enhances heart metabolism, a natural source of Iodine, Potassium (K), Magnesium (Mg), Calcium (Ca) and basic

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vitamins of cells (Mayer et al., 2011). Also, in includes several carbohydrates like Fucoidan, Laminine, Laminarin and Alginates (Kitamura et al., 1991).

Propylthiouracil (PTU) is a thyroinhibitory medication used to treat hyperthyroidism through preventing iodine oxidization (Chiao & Wang, 2000) . Moreover, this medication affects on the thyroid gland hormones or those in the blood stream where it prevents producing thyroid gland hormone by deoxidization of iodine. It prevents Thyroxin and Triiodothyronine formation. The common side effects are timidity, nausea, vomiting, burn, taste loss, numbness, headache, allergy, hair whitening, aplastic anaemia and leukopenia. Also, other symptoms include agranulocytosis and infections of throat, digestive system and skin with fever and decrease of blood platelets, which have an important role in blood coagulation (Sener et al., 2006).

Thyroid gland is one of the most important glands in the body. It is the only one that produces hormones and conservatives in the same gland for the time of need. The gland cells are the only one that able to absorb iodine (Ganong, 2001). Thyroid gland produces hormones as Thyroxin (T4) and Triiodothyronine (T3) that are derivatives of amino acid Tyrosine in response to Thyroid stimulating hormone (TSH) that secreted from anterior pituitary gland (Gregkelly, 2000). With the help of TPO enzyme, which is a glycoprotein includes hemes, it has the primary role to make thyroid hormones and this enzyme reflects the natural function of the gland and located on the top surface of follicle cells membrane (Ruf and Carayon, 2006).

Materials and Methods of Work:

1- Animals used

The study includes (60) male rats of (Rattus norvegicus) type. Each rat weights (170-180 gr.) and appropriate conditions are maintained, (20-21 C°), light (14 hrs), dark (10 hrs) and animals are given water and feed along the period of experimentation (42 days).

Experiment Design

The animals are divide into five groups in addition to the control one. All groups are equal in number of animals, (10) for each.

- Control group: it is given distilled water.
- (T1) dosed fucus vesiculosus of 35 mg/ kg concentration of body weight,
- (T2): propylthiouracil (PTU) of 15 mg/kg concentration of body weight is dosed
- (T3): fucus vesiculosus of 35 mg/ kg concentration of body weight is given for three weeks then (PTU) of 15 mg/kg concentration is dosed for the other three weeks.
- (T4): propylthiouracil (PTU) of 15 mg/kg concentration of body weight is dosed for three weeks then fucus vesiculosus of 35 mg/ kg concentration of body weight is given for three weeks.
- (T5) fucus vesiculosus and (PTU) are dosed conjonctions with the same concentrations for 42 days.

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-Molecular Study

-Quantitative Reverse Transcription Real- Time PCR (RT-qPCR)

Quantitative reverse transcription real- rime PCR (RT-qPCR) examination is conducted to measure mRNA transcript levels to show the TPO and TSH gene expression. Also, use GAPDH as a standard organizer gene to measure gene expression. The test is accomplished according to (Mygene Bioneer Korea) method.

-Real- Time PCR Data Analysis Method

Quantitative reverse transcription real- rime PCR (RT-qPCR) data is analyzed using Livak and Schmittgen (2001) method that depends on getting relative quantitative and absolute quantitative through the process of correcting and equating targeted genes with the control sample so that the results will have a biological meaning. Each sample should be equated and corrected with the control one to produce one level of relative change as shown in the equations below:

1- ΔCT(test)=CT(target , test) – CT (ref , test)
2- ΔCT(control)=CT(target , control) – CT (ref , control)
3- ΔDCT(test)=DCT(test) – Δ CT (control)
4- Gene expression Ratio = 2 - CTΔΔCT

Concentration and Purity of total RNA

The concentrations and purity of total RNA in pituitary gland tissues and thyroid gland tissues are high and sufficient to start testing PCR. The present results show that the optical density of wavelengths 260 and 280 nanometer is about (1,8 and 2,1), which is considered an evidence of total RNA purity for the samples included in the study.

Concentration of RNA in pituitary gland

The study results (Figure 1) reveal that there is a significant decrease ($P<0.05$) in the level of total RNA (monogram/microliter) in the tissues of pituitary gland in T1 but there is a significant increase in T2, T3 and T5. But there is no significant difference in T4 when compared with the control group.

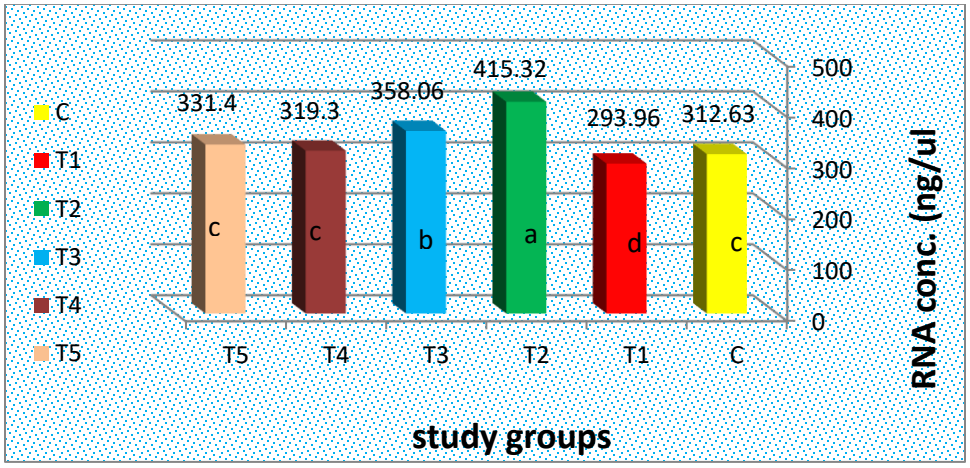

Figure (1) : Total RNA concentration in pituitary gland tissues of male rats

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1- RNA concentration in thyroid gland tissues

The study results (Figure 2) reveal that there is a significant increase in the level of total RNA (monogram/microliter) in T1, T3 and T5 while But there is no significant difference in T4 when compared with the control group.

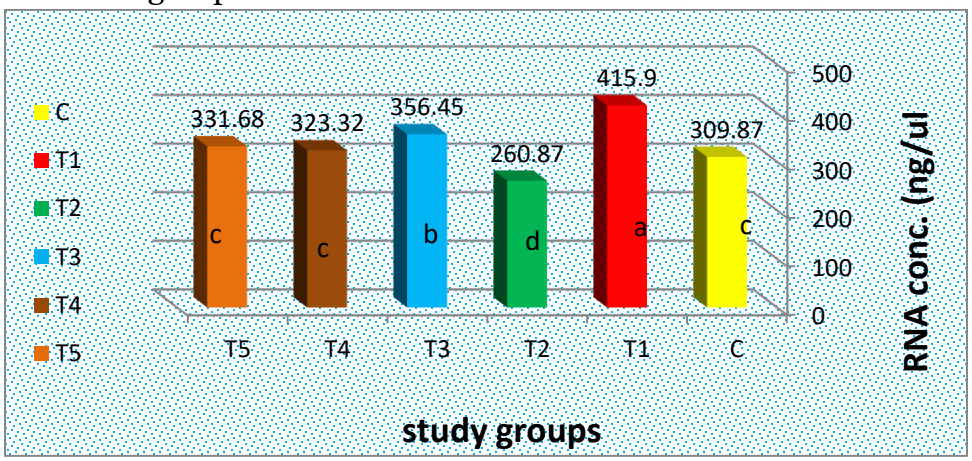

Figure (2): Total RNA concentration in thyroid gland tissues in male rats

- qPCR

it includes analyzing the reaction data of qPCR that depends on SYBR green. The process is divide into two parts: estimate the primer efficiency and the relative quantity for TSH and TPO levels of gene expression that are corrected by conservative genetic expression GapdH.

1- Primer efficiency estimation

The results of threshold cycle (TC) data have been calculated by amplification plot in qPCR device depending on exponential phase of flash signaling of SYBR green, which is integrated with gene primer studied in this study (TSH and TPO), and reacted with cDNA of mRNA of pituitary and thyroid glands tissues through amplification plot of threshold cycle. Linear regression is calculated depending on data points and the primer efficiency is deduced from linear slope as shown in (4-15) and (4-17).

2- Relative quantity of target gene expression

Target genes of the present study are (TSH and TPO) in the tissues of pituitary and thyroid glands. It is calculated by (2^(Λ-ΔΔct) equation, which is Livak and Schimittgen method. The process is to correct the target gene expression with the conservative gene expression because it is a correctional gene. Also, group C gene expression is considered a gene to control all target genes and the conservative gene GapdH. Livak equation includes several steps, the first one is to correct the number of threshold cycle of target gene TSH and TPO through correctional gene and for all treated genes in addition to the control group. The second step is to correct Δct for the treated group. Then the expression percentage is calculated in a process called fold change.

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2.1 Relative quantity for TSH gene expression in the pituitary tissues

The results of RT- qPCR reaction shown in Figure (4) that TSH gene expression in the pituitary tissues in T1 is increased ten times (10.458) above control group C (1.061). But T2 decreases by (0.752) when compared with the control group in T3 and T4, which is increased by (2.926) and (4.569) respectively when compared with the control group while there is no significant difference in T5 (1.269).

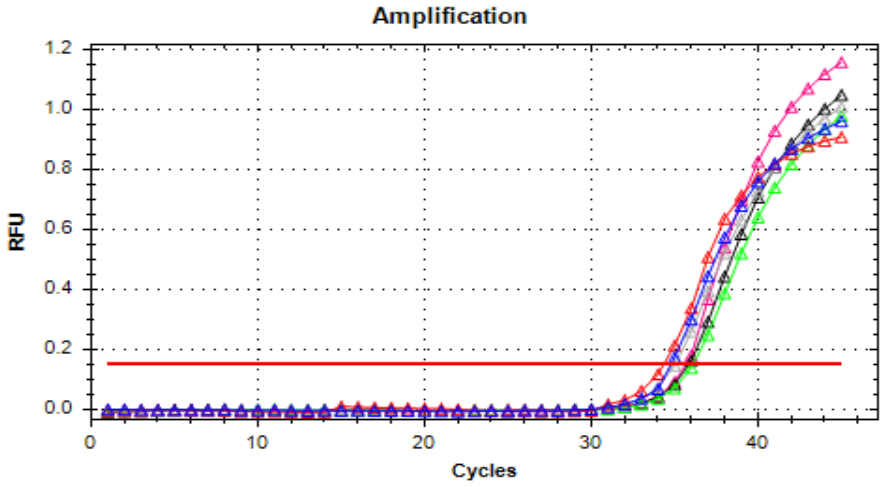

Figure (3 A): Real-Time PCR Amplification curve for GAPDH gene in pituitary tissues. The red curve represents T1, blue T2, green T3, Yellow is T4, pink is T5 and the black one is C group.

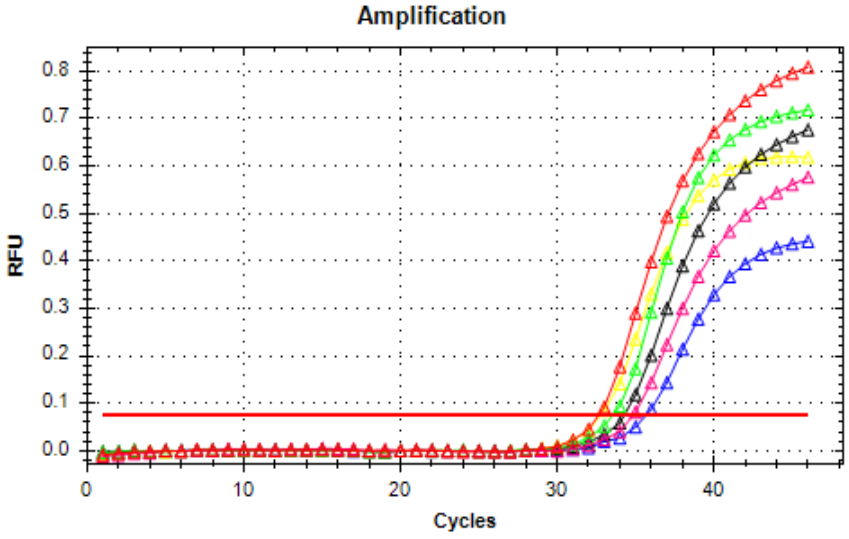

Figure (3 B) : Real-Time PCR Amplification curve for GAPDH gene in pituitary tissues. The red curve represents T1, blue T2, green T3, Yellow is T4, pink is T5 and the black one is C group.

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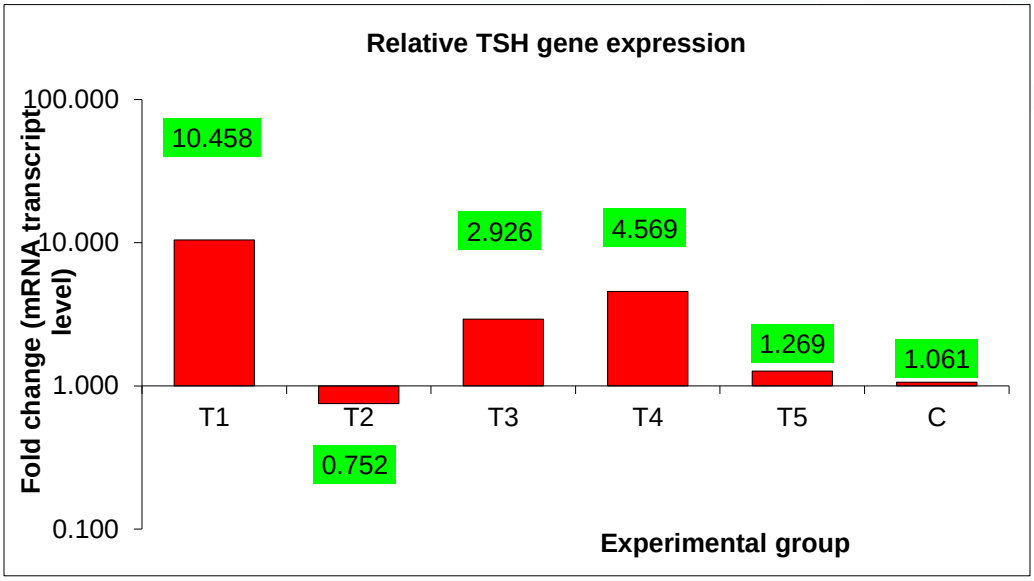

Figure (4) shows fold change of TSH gene in pituitary tissues of male rats treated with fucus vesiculosus and PTU including control group

2.2 Relative quantity of TPO gene expression in thyroid tissues

The results show (Figure 6) that there is a significant decrease in T1 by (0.882) when compared with the control group (1.056) while there is an increase by eight times (8.198), three times (3.253) and five times (5.978) in T2, T3 and T4 respectively when compared with control group. Also, there is an increase in T5 by (1.704) but it does not reach to significance level as compared with control group.

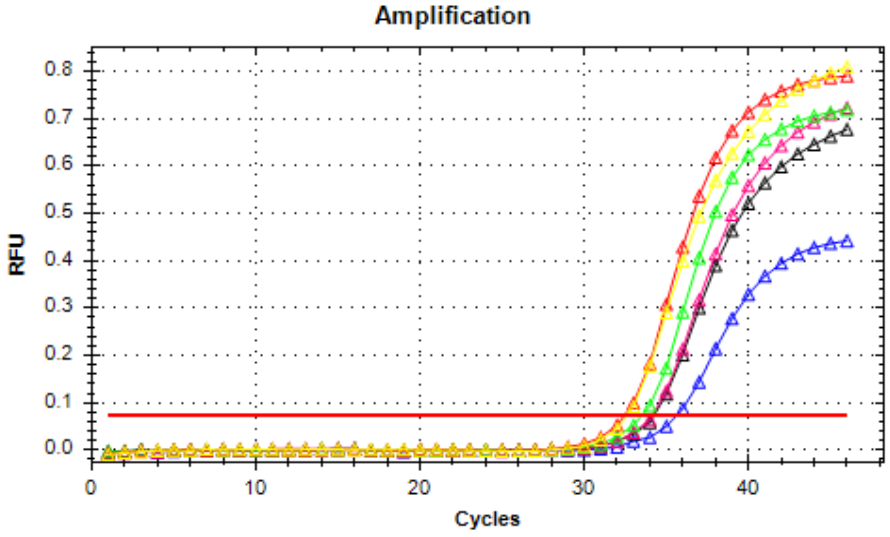

Figure (5 A): Real-Time PCR Amplification curve for GAPDH gene in thyroid tissues. The red curve represents T1, blue T2, green T3, Yellow is T4, pink is T5 and the black one is C group.

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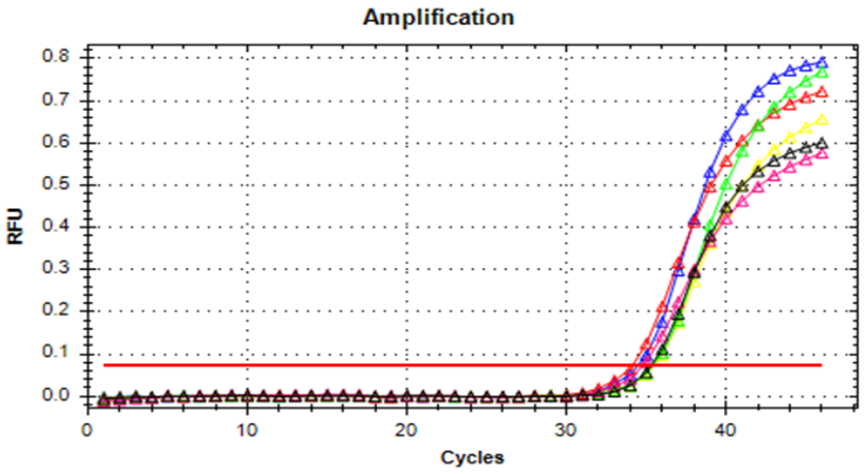

Figure (5 B): Real-Time PCR Amplification curve for TPO gene in thyroid tissues. The red curve represents T1, blue T2, green T3, Yellow is T4, pink is T5 and the black one is C group.

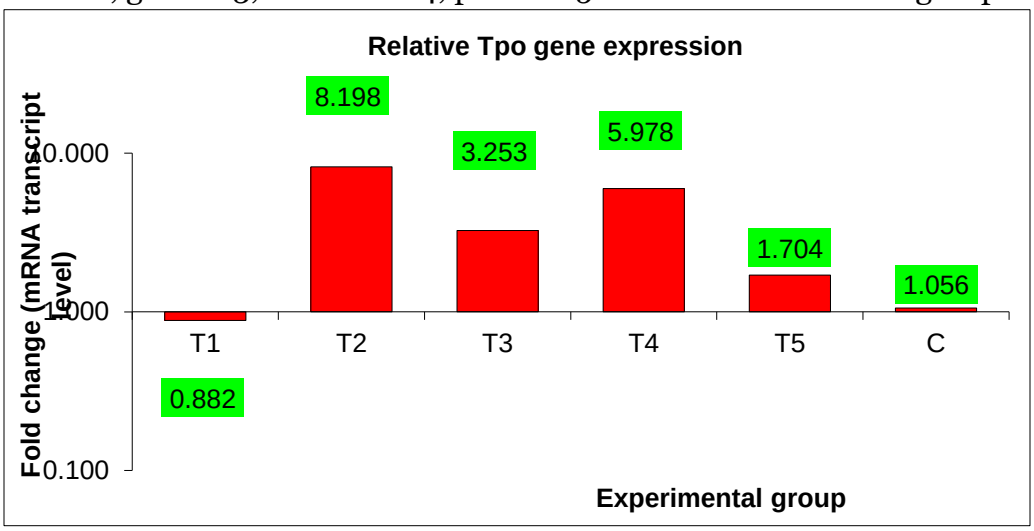

Figure (6): Shows fold change of TPO gene in pituitary tissues of male rats treated with fucus vesiculosus and PTU including control group

Discussion

1- Total RNA concentration in the tissues of thyroid and pituitary glands

The present study results reveal that there is a change in concentration level of RNA in the tissues of thyroid and pituitary glands where there is a decrease in RNA level in T1 that is treated with focus vesiculosus and there is an increase in total RNA level in T2, T3 and T5. But in T4, there is no significant difference when compared with control group. These changes up and down in pituitary tissues are attributed to the activity of nerve cells and secretion of inhibiting or releasing hormones and the activity of interior lobe of pituitary gland that secreted different stimulating hormones under the control of negative feedback mechanism. The present study focuses on studying Thyroid stimulating hormone (TSH), which is the major factor to motivate and organize thyroid gland secretion (Yen, 2001;

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Anderson, 2010) or the reason may be attributed to the effect of iodine on total RNA because the kelp contains high level of iodine so it will affect the function and formation of thyroid hormones (Steinmaus et al., 2007). As a result, thyroid hormones T3 and T4 increase and this affects the formation of TSH (Ladenson et al., 2000). TSH concentration is sensitive indicator for thyroid gland dysfunction (Fatourchi, 2009) of because of PTU, which enlarges thyroid gland. The reason is that thyroid gland is stimulated by pituitary gland where PTU inhibits the formation of thyroid hormones (Doerge and Sheehan, 2002; Udgat and Naik, 2007). In return, it affects total concentration of RNA because anti thyroid including PTU influences on gene expression and functions of some cells (Bandypadhyay et al., 2002).

The study results have referred to the increase of RNA concentrations in T1, T3, T4 and T5 while T2 has been treated with PTU. The reason is the change of total RNA concentrations in these groups and the change of creating protein, cells growth, discrimination, increase or decrease in protein expressions responsible of making thyroid hormones or disorder of TPO or TSH. It is well known that TSH is the organizer of gene expression of TPO in thyroid cells (Damante et al., 1989; Zarrilli et al., 1990).

2- Relative quantity of TSH and TPO gene expression in the tissues of thyroid and pituitary glands

The study results reveal that there is a significant increase in the level of TSH gene expression in tissues of pituitary gland but there is a decrease in the level of TPO gene expression in tissues of thyroid gland in T1 treated with focus vesiculosus and this result agrees with Calil- Silveira et al. (2016) for TSH. Though TSH increases in serum after being exposed to iodine, it does not affect TSH gene expression and protein. But what Calil- Silveira et al. (2016) agrees with the result of the present study as far as TPO enzyme is concerned, which is the major enzyme in creating thyroid hormones. This enzyme is created in Ribosomes then Golgi apparatus transfers it in a form of vesicles to the top end of follicle cell membranes. (Kuliawat et al., 2005; Ruf and Carayon, 2006) noticed that the decrease of gene expression of TOP mRNA and protein expression after doses of iodine as iodine the basic components of the kelp used in the present study (Arbaizav and LIorca,2011). It is known that TSH is the organizing Peptide to make and secrete thyroid hormones T3 and T4, which is secreted from the anterior lobe of pituitary gland and stimulated by TRH that secreted from hypothalamus. TSH stimulates T4 secretion from thyroid gland then T3 and T4 transforms in peripheral tissues. Then TRH-TSH- thyroid axis is called HPT- axis and through this axis T3 and T4 are maintained (Oshea and Williams, 2002; Costa et al., 2012; Schmaltz,2012; Stathatos, 2012). The kelp used in the study may have a role on HPT- axis due to the quantity of iodine in it. Several studies refer to the surplus of iodine inactivate HPT- axis (Braley-Mullen et al.,1999 ; Shi et al.,2014; Calil-Silveira et al.,2016). The study result agrees with (Li and Carayanniotis, 2007; Miyai et al., 2008) study who noted that excessive iodine leads to failure of thyroid work and weaken it hormones. This effect is confirmed through TSH and both units (Alpha and Beta). The increase of TSH leads to low thyroid hormones due to decrease of Gh mRNA content and increase Diodinase2 mRNA expression that is known as thyroid hormones organizer (Leonard et al.,1990; Silva et al., 2006). A previous study shows that treatment with iodine decreases the expressions of other

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genes in addition to TPO, which are (NIS and TSHR) but it increases of Pendred (PDS) expression (Suzuki et al.,1998; Sellitti and Suzuki, 2014).

Gene expression of TG, TPO, NIS and TSHR genes are organized depending on thyroid transcription factors (TTF). TSH represents the major organizer for TPO gene (Aza-Blanc et al.,1993; Ohno et al.,1997; Postiglione et al., 2002). The TPO promoter includes several locations of linking with TTF in thyroid, where TTF is of two types; TTF-1 and called (NKX2-1) it is a protein that has a role in the formation of organs especially thyroid and lungs (Guazzi et al.,1990; Kimura et al.,1996; Parlato et al., 2004). The second factor is Forhead box E1(FOXE1) it is protein that has the ability to identify and link to DNA of the promoter in TG and TPO. Also, it has the ability to organize genes transcription related to thyroid gland that leads to make thyroid hormones (Damante and Di Lauro,1994; Gudmundsson et al., 2009). The increase of TSH gene expression and the decrease of TPO gene expression in the animals treated with the kelp lead to genetic mutation and causes thyroid disorder eventually leads to low TPO and high TSH (Castanet etal.,2002;Castanet and Polak,2010;Rastogi and LaFranchi,2010). Beside the direct effects of iodine on thyroid and TSH, these changes may lead to changes of genes including thyroid hormones. Also, it may change the levels of glycosylation with TG in follicles (yen, 2001).

The study results shows the decrease of TSH gene expression in the tissues of pituitary gland of T2 treated with PTU while TPO gene expression increases in the tissue of thyroid gland of T2, T3 and T4 when compared with the control group. PTU is an anti-thyroid and used basically to treat Grave's disease which enlarges thyroid gland (Moriyama etal.,2007;Manna etal.,2013). The effects of PTU is inside the cell in which it inhibits creating T3 and T4. But the action of this medication outside thyroid gland is to prevent transforming T4 into T3 (Cooper,1984; Cooper, 2005). The study results agree with Maenhaut et al., (1992). They noted that using anti- thyroid leads to increase the levels of Tg and TPO. Also, the results agree with (Leer etal.,1991;Isozaki etal.,1991; Sugawara etal.,1999) who mentioned that anti-thyroid has changed some gene expressions and MMI and PTU increase in Tg expression and other expressions related to thyroid and the reason is the decrease of TSH gene expression is the Cytokines in pituitary gland and hypothalamus. Because Cytokines inhibits TSH secretion and TSH is affected by other hormones like Oestrogenes and Glucocorticoids and growth hormones (Jackson, 1982). Pau et al., (2012) mentioned that anti- thyroid inhibits producing some hormones that prevents producing other hormones related TSH secretion and decreases its required quantity, or there is a kind of disorder of oxidization level and anti-oxidant due to PTU treatment. This case leads to increase Reactive oxygen species (ROS) and these reactive molecules are existed in all cells and tissues of low percentage. But when it is existed in high percentage, it causes severe cells damage and biomolecules like proteins, fat and nuclear acids (Halliwell,2007). Moreover, several studies have proved that through Cyclic adenosine monophosphate(cAMP), TSH increases trnascrition of mRNA of some genes like Tg and TPO (Gerard et al.,1989; Pohl et al.,1990). In the present study, TSH gene expression is decreased due to PTU treatment, which affects TSHR receptors because TSH is responsible for activating these receptors and this decrease is the reason of cAMP levels inside the cell. Consequently, it causes several mutations that affect TSH and TPO levels or these changes may be in thyroid stimulating hormone and Thyroid Peroxidase Enzyme due to unknown mechanisms like non-genetic factos.

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