Estimation of Galectin-3, cyclooxygenase-2 and thyroid hormones in papillary thyroid carcinoma

Zahraa Ali Jaafer[1], Zaizafoon Nabeel Nasif[2], Muntadher Salih Sultan[3]
[1,2,3]Chemistry Department, College of Science, Mustansiriyah University, Iraq.
Email: zahraaali568@gmail.com

Abstract
Thyroid cancer is one of the most critical endocrine cancers, and ismore common in women than in men, but the associated causes of these differences are not fully understood. Serum biomarkers were tested in Iraqi thyroid cancer patients as part of this study's objective. Galectin-3, cyclooxygenase-2 (COX-2), thyroid stimulating hormone (TSH), Thyroxin (T4) and triiodothyronine (T3), could be useful in the identification, screening, diagnosis and follow-up of thyroid cancer patients. 60 thyroid cancer patients' anthrobiological features were found to have considerable abnormalities in all traits. The results showed a significant increase ($p < 0.05$) in the mean value of Triiodothyronine (T3) (2.418±1.153,0.664±1.206) Thyroxine (T4) (10.380±3.483,6.967±2.221) Thyroid-stimulating hormone (TSH) (7.466±16.119,1.286±1.168) COX2(1.828±0.725,2.663±0.985) Galectin by Elisa (145.243±180.9,46.441±27.874) levels in patients compared to the control group. Compared to the control group, the estimates of variation % results for patients are more exact. (ROC)(AUC) was measured to evaluate sensitivity and specificity. The higher the sensitivity, the more likely it is that the disease carriers will be classified correctly, while specificity cares about healthy people. T3 and Galectin-3 have high sensitivity. Pearson's correlation coefficient between all measured parameters shows there is no correlation significance.
Keyword: thyroid cancer, Galectin-3, Cyclooxygenase-2, TSH, T4, T3.

1. Introduction

The thyroid gland is a vascularized organ located anteriorly in the neck, between the C5 and T1 vertebrae, between the platysma, sternothyroid, and sternohyoid muscles. Men's thyroids weigh 15–20 g, whereas women's thyroids weigh around 1 g and increase by about 1 g per year until age 15. The thyroid grows by about 1 g each year until age 15. It's an H-shaped parenchymal organ that's soft and reddish in color, with two lobes (one on each side) connected by an isthmus (Fig. 1). The lobes are around 4cm long, 2cm wide, and 2–3cm thick, with the thickest lobes being the thickest. The isthmus is 2 centimeters wide, 2 centimeters high, and 2–6 millimeters thick. It is positioned lateral to the inferior constrictor muscle and posterior to the sternothyroid muscle, while the inferior horn extends from the fifth or sixth tracheal ring levels. The posterior section of the gland overlaps the carotid sheath and its various parts. There are around half the population who are born with an isthmus or lobe with an ascending pyramidal lobe (Morgagni's or Lalouette's pyramid) facing to the left. [1].

The sternocleidomastoid and strap muscles surround the thyroid from the front and the deep cervical fascia layers from the side. Thyroid lobes and lobules are separated by septae in the true thyroid capsule, which is securely linked to the gland. The posterior layer of the thyroid capsule is thick. Berry's posterior suspensory ligament condenses the deep cervical fascia's middle layer to connect the thyroid lobes to the cricoid cartilage and the first two tracheal rings. In most people, there are four parathyroid glands (two superior and two inferior), each about the size of a grain of rice and located on the posterior side of the lateral lobes.[2].

Thyroid cancer is the most common type of endocrine tumor. Thyroid cancer was diagnosed in 11,470 men and 36,550 women in the United States in 2011, with 1,740 men and women dying from the disease [3]. Since its discovery, thyroid carcinoma has long been considered to be a disease with an excellent prognosis. According to SEER data, the overall survival rate has remained stable in recent decades between 90% and 95%. About 90% of all thyroid malignancies are papillary thyroid carcinomas, a low-risk histological type. The large subclinical thyroid cancer reservoir can now be detected thanks to the increase in sensitivity of thyroid cancer diagnostic methods, such as ultrasonography and fine-needle aspiration. On the other hand, patients with thyroid cancer might go years with no symptoms while the illness remains undetected and untreated. According to pathologists, thyroid cancer is a common postmortem result, and research indicated that nearly 9% of cadavers had thyroid cancer, even if the cause of death was not thyroid cancer [4]. Many thyroid cancer patients will live for a long time if they are properly treated, but this does not rule out the risk of death from other causes. Thyroid cancer patients and their families must take into account the emergence of new causes of death while evaluating their prognosis. providing doctors with an effective predictor of mortality risk and a more accurate prediction of prognosis for thyroid cancer patients. [3].

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone that is made by the anterior pituitary gland.

doi.org/10.31838/hiv22.02.651 Received: 18.04.22, Revised:30.06.22, Accepted: 01.08.22

It is the main thing that makes the thyroid gland make thyroid hormone. It also makes thyroid follicular cells multiply, which causes the thyroid to get bigger. The hypothalamic-pituitary axis controls how much TSH is made. Neurons in the hypothalamus release a hormone called thyroid-releasing hormone (TRH). This hormone tells the anterior pituitary thyrotrophs to release TSH. In response, TSH tells the thyroid follicular cells to make T3 or T4 thyroid hormones. Triiodothyronine is the form of thyroid hormone that works (T3). Most T3 comes from the conversion of T4 to T3 in the periphery, which makes up only 20% of the hormone made. Over 80% of the hormone that is released is tetraiodothyronine (T4), which is also called thyroxine or T4. De-iodination happens when it goes back into the bloodstream, making T3. The anterior pituitary can then get a negative feedback loop from T4 and T3, with high T3/T4 levels causing less TSH to be released and low T3/T4 levels causing more TSH to be released.[5].

Both tetraiodothyronine (T4) and triiodothyronine (T3) are essential hormones for human metabolism, and the thyroid gland is responsible for their production (T3). The first step in the synthesis of thyroid hormones is iodine metabolism, which consists of the following three steps: active iodide transport into the thyroid; iodide oxidation; and subsequent iodination of tyrosyl residues of thyroglobulin (Tg) to produce iodotyrosines, monoiodotyrosine (MIT) and diiodothyrosine (DIT). Both T4 and T3 contain iodine that has been oxidized as well as tyrosyle residues, which are aromatic amino acids. A deficiency in thyroid iodine can be caused by dietary inadequacies, a malfunctioning thyroid, or a condition of the brain and pituitary gland that prevents them from producing adequate thyroid stimulating hormone. This deficiency can lead to hypothyroidism, which can have serious consequences (TSH). Thyroid hormone synthesis begins with iodine oxidation, which is mediated by the thyroperoxidase enzyme (TPO), which is triggered by TSH and necessary for the formation of MIT and DIT. Following the MIT and DIT coupling reactions, 4 and T3 are produced on Tg. Final production of thyroid hormones is activated by thyroid stimulating hormone (TSH)-induced Tg pinocytosis and subsequent lysosomal function, both of which occur in the follicular area. A negative feedback link between T4 and T3 and TSH governs the manufacture of these hormones externally, while increasing iodine within the thyroid gland regulates them internally. TPO and hydrogen peroxide (H2O2) production, both of which are critical for iodine oxidation, are considered to be inhibited by the increasing iodine level in the thyroid gland, hence limiting thyroid hormone synthesis. When serum T4 and T3 concentrations fall, healthy people's production of T4 and T3 begins again. Clinical symptoms and thyroid hormone insufficiency eventually occur in thyroid disorders produced by one of the following mechanisms.[6].

An enzyme family called COX is responsible for the biosynthesis of prostaglandins and thromboxane by converting arachidonic acid (AA) into prostaglandin H2 (PGH2). Many different physiological and pathological effects of bioactive lipids can be traced back to these molecules. COX enzyme inhibition is one of the mechanisms through which NSAIDs exert their pharmacological effects [7]. Different COX isoforms were found to be encoded by two distinct genes. COX-1 is expressed throughout the body and plays a critical role in the production of PGs that perform basic housekeeping functions. Carbamazepine 2 (COX-2), a cytokine, mitogen or endotoxin-activated enzyme, is the most common type of COX-2 inducible enzyme (together with COX-1). Between the two enzymes, there is a high degree of amino acid sequence and structural homology (rmsd 1.0). An anti-inflammatory and analgesic effect could be achieved by inhibiting COX-2, which was found in the early 1990s and has a different expression profile than COX-1 [9]. The research shows that COX-2 inhibition is responsible for the anti-inflammatory effects of standard NSAIDs, while COX-1 inhibition is responsible for the ulcerogenic side effects. The non-targeted suppression of COX-1 and COX-2 by NSAIDs induces considerable gastrointestinal damage at typical clinical doses. COX-2 inhibitors like celecoxib and rofecoxib have since been employed to test the COX-2 theory in animal arthritic models and human clinical studies. [8].

Galectins are a family of proteins that recognize and bind galactosides to cellular glycoproteins and glycolipids [10]. In the galectin family, Gal-3 is the 31-kilodalton (kDa) member with the most unique structure. One of the few components in the cell with a pentameric structure, Gal-3 is able to crosslink glycoproteins on the cell surface and create new lattices that are critical for cellular signaling and receptor endocytosis. Gal-3's C-terminal domain contains a carbohydrate-recognition region that enables the lectin to bind to its specific carbohydrate [11]. [10]. Several amino acids, such as proline, tyrosine, and glycine, can be found in the N-terminal domain, which is critical for cellular signaling and receptor stability [12, 13]. As a result of its inability to form pentamers, Gal-3's extracellular activities are lost upon proteolytic cleavage of its N-terminal domain. [14] Serine-6 and Serine-12 residues in Gal-3's N-terminal domain can additionally phosphorylate Gal-3. [15] In addition to the nucleus and cytoplasm, Gal-3 has also been discovered in the cytosol and extracellular space. Tumor growth in patients with thyroid cancer has also been connected to the expression of the gene that controls apoptosis, cell movement, and T-cell proliferation [12, 16]. Cellular physiology may shed light on Gal-3's importance in thyroid cancer.

II. EXPERIMENTAL PART

Collection of Blood Sample

Serum samples were taken at Al-Amal hospital for tumors / Baghdad from 9:00 p.m. to 12:00 a.m. in October 2021 from 60 thyroid cancer patients and 30 healthy people. Using a disposable syringe, blood was drawn from the anterior cubital vein of each subject and transferred to a clean simple gel tube. Within 15 minutes of collecting blood, the serum was centrifuged and divided into three micropipette sections into Eppendorf tubes and stored at -20°C for biochemical analysis.

2. Kits

1.1Estimation of (TSH), (T3), (T4) and Galectin-3

Each of thyroid stimulating hormone (TSH), Triiodothyronine(T3) and thyroxin(T4) by mini vides were supplied by (Human/Germany), Galectin-3 Elisa kit was supplied by (Shanghai \China) It's been started to figure out using the methods associated.

3. 2. Statistical Analysis

In order to analyze the data, SPSS-28 was utilized. A descriptive analysis was performed on each parameter, and the results were expressed as the mean standard deviation (SD). An independent-sample t-test was used to compare the control and sick groups' mean values. For this study, Pearson's rank correlation coefficient analysis was used to determine the relationships among each of the variables evaluated.

4. Result and discussion

1.2 Estimation of COX-2 Activity:

Colorimetric assays for peroxidase activity in serum from thyroid cancer patients [9] are used to evaluate the activity of COX-2 enzyme. This technique uses enzymes to monitor the hydrogen peroxide oxidation of tetramethylphenylenediamine (TMPD) catalyzed by hydrogen peroxide (H2O2). We looked for a blue response by reading 610 nm. The amount of enzyme required to convert one mole of hydrogen peroxide to the product is what is known as one unit of activity in testing.

Thyroid cancer continues to be a big problem, with poor detection, ineffective therapy, and a high death rate. Patients with thyroid cancer are the subject of this study. Galectin, thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxin(T4) were all examined to see if they played a role in the development of papillary thyroid cancer (PTC). COX-2 levels were compared to those of healthy individuals. This research examines and summarizes the anthropobiological parameters of 60 thyroid carcinoma patients (Table 1). The average age of the patients was 45.0 years, and all of the patients' and control group's characteristics were statistically different from each other.

Table 1. A comparison of the morphological characteristics of thyroid cancer patients and control groups.

		Thyroid carcinoma(60)		Healthy Control(30)		P value
		No	%	No	%	
Age (years)	<30years	7	11.7	-	-	0.0001*
	30---39	8	13.3	13	43.3	
	40---49	20	33.3	17	56.7	
	=>50years	25	41.7	-	-	
	Mean±SD (Range)	45.0±9.1(25-59)		39.1±3.5(31-45)		0.0001#
Gender	Male	19	31.7	13	43.3	0.276
	Female	41	68.3	17	56.7	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant difference between two independent means using Students-t-test at 0.05 level.						

60 patients had preoperative testing for Galectin, TSH, T3, and Thyroxin (T4) in the therapeutic phase of (PTC). The mean values of each serum factor examined were used to calculate the parameter levels, which are summarized in Table 2.

Table 2.The Galectin (ng\ml), Thyroid-stimulating hormone (TSH) (µg/mL),Thyroxine (T4) (µg/dL),Triiodothyronine (T3) (µg/dL), COX-2

	Thyroid carcinoma(60)	Healthy control(30)	
Triiodothyronine (T3) (µg/dL)	2.418±1.153 (0.80-6.90)	0.664±1.206 (0.13-4.60)	0.0001#
Thyroxine (T4) (µg/dL)	10.380±3.483 (1.90-18.00)	6.967±2.221 (1.70-12.00)	0.0001#
Thyroid-stimulating hormone (TSH) (µg/mL)	7.466±16.119 (0.04-70.00)	1.286±1.168 (0.60-7.00)	0.0039#
COX-2	1.828±0.725 (0.580-3.700)	2.663±0.985 (1.000-4.800)	0.0001#
Galectin-3 by Elisa (ng/mL)	145.243±180.945 (47.375-856.346)	46.441±27.874 (4.131-94.565)	0.004#

#Significant difference between two independent means using Students-t-test at 0.05 level.

Results showed a significant increase ($p< 0.05$) in the mean value of Galectin-3, TSH, T3, and T4 activity in patients compared to the control group. Except COX-2 showed a significant decrease these findings were in agreement with many studies. Among thyroid cancer patients, serum levels were found to be higher than those of healthy individuals. Differentiated thyroid tumors (DTC)are associated with elevated TSH levels. To prove this connection, we'll need to conduct a survey. When comparing the mean TSH levels of the case and control groups, it was found that those in the case group had a substantially higher TSH level than those in the control group (7.466–16.4119, 1.168–1.286, P=0.039). Thyroid carcinogenesis can be accelerated by a high TSH level in the normal range, which is a risk factor in and of itself for DTC patients . Patients with thyroid nodules who have elevated TSH levels could be used as a diagnostic tool to identify high-risk patients who require further investigation and/or surgery. In comparison to the general population, people with DTC have significantly higher TSH levels. We found that a higher TSH level within the normal range was an independent predictor of the presence of DTC, regardless of age, gender, or family history of thyroid cancer. In this study, higher TSH levels were not associated with a more advanced tumor stage or a larger tumor size. TSH stimulates the generation and release of thyroid hormones, which aids in thyroid growth [17]. On benign nodules and DTC, thyrocytes possess TSH receptors, which interact with TSH to stimulate the thyroid's proliferation[18]. TSH secretion is suppressed by administering exogenous thyroid hormone at supraphysiologic dosages. TSH suppression decreases nodule formation and development [19]and increases overall survival in high-risk DTC patients [20].

The levels of T3 and T4 hormones were shown to be substantially linked with thyroid cancer in this study. Thyroid hormones (T3 and T4) affect a variety of physiological functions, including cell proliferation. They can serve as both growth factors and inhibitors of cell growth, which makes them particularly interesting in terms of tumor and cancer cell proliferation. Recent clinical evidence shows that hypothyroidism is linked to a statistically significant increased risk of hepatocellular carcinoma [21], while also being linked to a low risk of breast cancer [22] and a longer life expectancy of glioblastoma multiform patients [23]. Deiodinase I and II (which convert T4 to T3), as well as deiodinase III, regulate the local amount of thyroid hormones (which degrade both T3 and T4)[24]. Thyroid malignancies' clinical behavior is thought to reflect the innate transcriptional activity of mutant genes as well as the trophic effects of circulating pituitary thyrotropin on tumors (TSH). L-thyroxine (T4), a thyroid hormone, has been demonstrated to promote cancer proliferation in a variety of distinct ways. The role of T4 as a circulating trophic factor for differentiated (papillary and follicular) thyroid tumors is discussed briefly in this article. Given T4's ability to stimulate cancer growth in differentiated thyroid tumors.

Galectin-3 (Gal-3) plays a key role in cell proliferation in both normal and pathologic tissues, adhesion, differentiation, angiogenesis, and death. Gal-3 may play a role in tumor cell transformation, migration, invasion, and metastasis, according to study. Gal-3 is gaining traction as a novel biomarker for the

detection, therapy, and prognosis of various types of cancer. Gal-3 appears to have a wide range of cancer-type-specific pathways. It will be easier to use these multifunctional properties if we understand and clarify the molecular mechanisms involved. [25] and [26] indicate that Galectin-3 overexpression may induce neoplastic transformation. By blocking the expression of galectin-3 in human thyroid papillary carcinoma cells, antisense cDNA reduced anchorage-independent cell proliferation [27]. When normal thyroid cells were transfected with the cDNA of galectin-3, gene expression, contact inhibition and serum-independent growth were all altered [27]. Malignant thyroid cells' aberrant phenotypes are maintained by galectin-3 expression, according to these findings. The interaction of galectin-3 with oncogenic K-Ras has been shown to have a role in the molecular process of galectin-3-mediated transformation [25].

Tumorigenesis may be aided by cyclooxygenase-2 (COX-2), an inducible version of the enzyme that transforms arachidonic acid into prostanoids. Thyroid carcinogenesis and cyclooxygenase 2 (COX-2) expression were studied using immunohistochemistry, and COX-2 levels steadily reduced in papillary cancers. A possible function for COX-2 overexpression in lymphocytic thyroiditis and thyroid cancer inflammation has been hypothesized. The incidence of sporadic colorectal cancer is greatly reduced by NSAIDs and COX inhibitors, two classes of nonsteroidal anti-inflammatory drugs. These findings demonstrate a constant up-regulation of COX-2 expression during the progression of lymphocytic thyroiditis and papillary carcinoma, as well as the importance of COX-2 overexpression for the development of thyroid tumors. Papillary cancer had COX-2 expression. It is possible that COX-2 may play a role in the early stages of thyroid and colorectal tumors, as the enzyme was found in papillary carcinomas. Epithelial cell proliferation is increased by COX-2 acting on arachidonic acid, which produces prostaglandins [28]. Moreover [29], a decrease in COX-2 is associated with a reduction in cell apoptosis resistance. However, COX-2 inhibitors cause apoptosis and decrease cell proliferation[31][32]. Furthermore, a reduced level of vascular endothelial growth factor is expressed in mice with COX-2 suppression or deletion, which reduces angiogenesis [31]. Tumors in the blood arteries of thyroid neoplasms show enhanced vascular endothelial growth factor expression. COX-2 inhibitors, like nonsteroidal anti-inflammatory drugs and colorectal carcinogenesis, may prevent thyroid tumor formation or progression, according to our current data.

By observing the results of the (ROC), we found that all the tests gave results of high sensitivity, except forCOX-2, which decreased due to the fact that patients continue to take the treatment, and this corresponds to our previous results, in addition to the area under the curve (AUC)The results were excellent as the T3 (0.9) and both Galectin-3,T4 (0.8) as shown in Table 3 and Figure 1. Table 4 reveals that there is no correlation between the pearson's correlation coefficients of all measured parameters..

Table 3 :Area Under the Curve (AUC) for all parameters

Test Result Variables	Area Under the Curve (AUC)	Std. Error	P value	95% Confidence Interval	
				Lower Bound	Upper Bound
Triiodothyronine (T3) (µg/dL)	0.924	0.043	0.0001	0.840	1.000
Thyroxine (T4) (µg/dL)	0.820	0.047	0.0001	0.728	0.912
Thyroid-stimulating hormone (TSH) (µg/mL)	0.559	0.060	0.367	0.441	0.677
COX2	0.745	0.056	0.0001	0.636	0.855
Galectin by Elisa(ng/mL)	0.835	0.046	0.0001	0.744	0.926

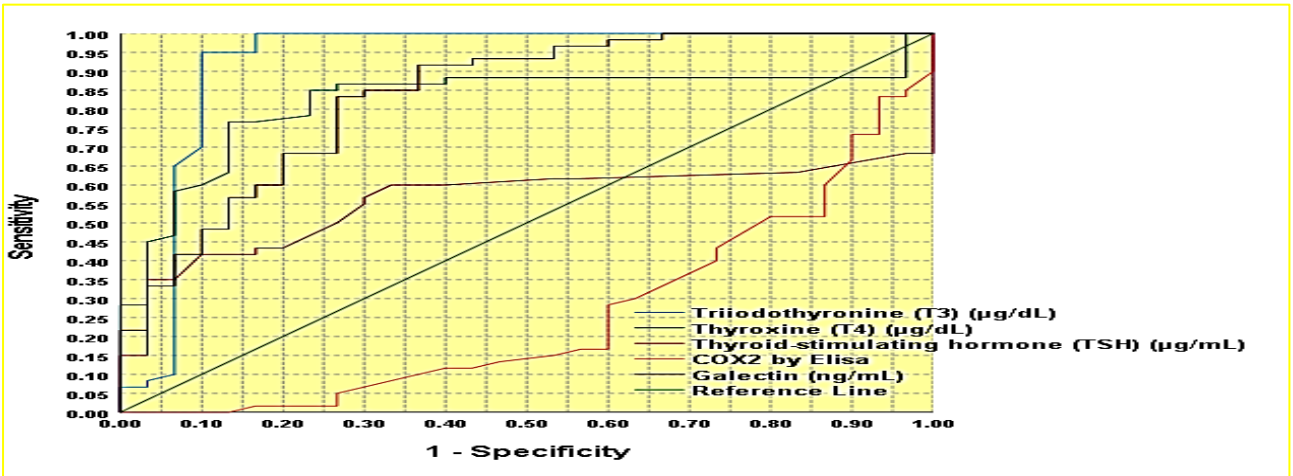

Figure 1: RecevierOperatic

caracteristis (ROC) curve

Table 4: pearson's correlations between variables in TC the patients group.					
		Thyroid carcinoma (n=60)		Healthy controls (n=30)	
		COX-2	Galectin by Elisa(ng/mL)	COX-2	Galectin by Elisa(ng/mL)
Age (years)	r	-0.113	-0.012	-0.204	-0.005
	P	0.390	0.930	0.279	0.981
Triiodothyronine (T3) (µg/dL)	r	0.205	-0.034	-0.097	0.059
	P	0.115	0.797	0.609	0.755
Thyroxine (T4) (µg/dL)	r	0.211	0.231	-0.200	-0.293
	P	0.105	0.075	0.290	0.117
Thyroid-stimulating hormone (TSH) (µg/mL)	r	-0.143	-0.137	0.296	-0.324
	P	0.277	0.298	0.112	0.080
COX-2	r	-	0.007	-	-0.162
	P	-	0.959	-	0.393
Galectinby Elisa (ng/mL)	r	0.007	-	-0.162	-
	P	0.959	-	0.393	-
*Correlation is significant at the 0.05 level.**Correlation is highly significant at the 0.01 level.					

5. Conclusion

Despite the fact that different studies' findings often disagree, T3 remains a critical criterion for properly monitoring thyroid cancer patients. The activities of Galectin-3, T4, TSH, and COX-2 also have a major prognostic component that is linked to the diagnosis of disease and the prediction of cancer risk. Positive tests for T3 and Galectin show that carriers of the disease have a high detection rate. This aggressive thyroid carcinoma still need the use of the most effective early detection approach..

References:

[1] S. Benvenga, G. Tuccari, A. Ieni, and R. Vita, *Thyroid gland: Anatomy and physiology*, 2nd ed., no. January. Elsevier Inc., 2018.

[2] M. Nilsson and H. Fagman, "Development of the thyroid gland," *Development*, vol. 144, no. 12, pp. 2123–2140, 2017.

[3] N. Howlader *et al.*, "SEER cancer statistics review, 1975–2016," *Natl. Cancer Inst.*, vol. 1, 2019.

[4] L. Bondeson and O. Ljungberg, "Occult thyroid carcinoma at autopsy in Malmö, Sweden," *Cancer*, vol. 47, no. 2, pp. 319–323, 2015.

[5] Y. Pirahanchi, F. Toro, and I. Jialal, "Physiology, thyroid stimulating hormone," 2018.

[6] C. Penel, D. Gruffat, C. Alquier, A. Benoliel, and O. Chabaud, "Thyrotropin chronically regulates the pool of thyroperoxidase and its intracellular distribution: a quantitative confocal microscopic study," *J. Cell. Physiol.*, vol. 174, no. 2, pp. 160–169, 2018.

[7] A. S. Kalgutkar, B. C. Crews, S. Saleh, D. Prudhomme, and L. J. Marnett, "Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors," *Bioorg. Med. Chem.*, vol. 13, no. 24, pp. 6810–6822, 2005.

[8] W. L. Smith, "DeWitt DL, Garavito RM," *Cyclooxygenases Struct. Cell. Mol. Biol. Annu Rev Biochem*, vol. 69, pp. 145–182, 2000.

[9] J. L. Masferrer *et al.*, "Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic.," *Proc. Natl. Acad. Sci.*, vol. 91, no. 8, pp. 3228–3232, 2014.

[10] X. Yao, Y. Peng, L. Xu, L. Li, Q. Wu, and P. Xiao, "Phytochemical and biological studies of Lycium medicinal plants," *Chem. Biodivers.*, vol. 8, no. 6, pp. 976–1010, 2019.

[11] H.-Y. Chen *et al.*, "Role of galectin-3 in mast cell functions: galectin-3-deficient mast cells exhibit impaired mediator release and defective JNK expression," *J. Immunol.*, vol. 177, no. 8, pp. 4991–4997, 2016.

[12] B. Mehul, S. Bawumia, S. R. Martin, and R. C. Hughes, "Structure of baby hamster kidney carbohydrate-binding protein CBP30, an S-type animal lectin.," *J. Biol. Chem.*, vol. 269, no. 27, pp. 18250–18258, 2014.

[13] S. Ramasamy, S. Duraisamy, S. Barbashov, T.

Kawano, S. Kharbanda, and D. Kufe, "The MUC1 and galectin-3 oncoproteins function in a microRNA-dependent regulatory loop," *Mol. Cell*, vol. 27, no. 6, pp. 992–1004, 2017.
[14] J. Dumic, S. Dabelic, and M. Flögel, "Galectin-3: an open-ended story," *Biochim. Biophys. Acta (BBA)-General Subj.*, vol. 1760, no. 4, pp. 616–635, 2016.
[17] T. Kimura, "Van Keymeulen A, Golstein J, Fusco A, Dumont JE, Roger PP," *Regul. Thyroid cell Prolif. by TSH other factors a Crit. Eval. Vitr. Model. Endocr Rev*, vol. 22, pp. 631–656, 2010.
[18] N. R. Farid, Y. Shi, and M. Zou, "Molecular basis of thyroid cancer," *Endocr. Rev.*, vol. 15, no. 2, pp. 202–232, 2014.
[19] A. Persichetti *et al.*, "Predictive value of malignancy of thyroid nodule ultrasound classification systems: a prospective study," *J. Clin. Endocrinol. Metab.*, vol. 103, no. 4, pp. 1359–1368, 2018.
[20] D. S. A. McLeod *et al.*, "Prognosis of differentiated thyroid cancer in relation to serum thyrotropin and thyroglobulin antibody status at time of diagnosis," *Thyroid*, vol. 24, no. 1, pp. 35–42, 2014.
[21] M. M. Hassan *et al.*, "Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States," *Hepatology*, vol. 49, no. 5, pp. 1563–1570, 2019.
[22] M. Cristofanilli *et al.*, "Thyroid hormone and breast carcinoma: primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma," *Cancer Interdiscip. Int. J. Am. Cancer Soc.*, vol. 103, no. 6, pp. 1122–1128, 2015.
[23] J. Hercbergs, C. Suh, and B. Reddy, "Propylthiouracil-Induced Chemical Hypothyroidism with High-Dose Tamoxifen Prolongs Survival with Increased Response Rate in Recurrent High Grade Glioma," in *Proceedings of the American Association for Cancer Research. 93rd Annual Meeting San Francisco, Abstract*, 2002, no. 2442, p. 43.
[24] J. Ko¨ hrle, "The selenoenzyme family of deiodinase isozymes controls local thyroid hormone availability," *Rev. Endocr. Metab. Disord.*, vol. 1, pp. 49–58, 2010.
[25] G. Elad-Sfadia, R. Haklai, E. Balan, and Y. Kloog, "Galectin-3 augments K-Ras activation and triggers a Ras signal that attenuates ERK but not phosphoinositide 3-kinase activity," *J. Biol. Chem.*, vol. 279, no. 33, pp. 34922–34930, 2014.
[26] F.-T. Liu and G. A. Rabinovich, "Galectins as modulators of tumour progression," *Nat. Rev. Cancer*, vol. 5, no. 1, pp. 29–41, 2005.
[27] Y. Takenaka *et al.*, "Malignant transformation of thyroid follicular cells by galectin-3," *Cancer Lett.*, vol. 195, no. 1, pp. 111–119, 2013.
[28] G. J. Tsioulias, M. F. Go, and B. Rigas, "NSAIDs and colorectal cancer control: promise and challenges," *Curr. Pharmacol. reports*, vol. 1, no. 5, pp. 295–301, 2015.
[29] H. Sheng, J. Shao, J. D. Morrow, R. D.
[15] H. C. Gong *et al.*, "The NH2 terminus of galectin-3 governs cellular compartmentalization and functions in cancer cells," *Cancer Res.*, vol. 59, no. 24, pp. 6239–6245, 2012.
[16] J. J. Lee *et al.*, "Predicting cancer development in oral leukoplakia: ten years of translational research," *Clin. Cancer Res.*, vol. 6, no. 5, pp. 1702–1710, 2020.
Beauchamp, and R. N. DuBois, "Modulation of apoptosis and Bcl-2 expression by prostaglandin E2 in human colon cancer cells," *Cancer Res.*, vol. 58, no. 2, pp. 362–366, 2018.
[30] S. Battu, M. Rigaud, and J. L. Beneytout, "Resistance to apoptosis and cyclooxygenase-2 expression in a human adenocarcinoma cell line HT29 CL. 19A.," *Anticancer Res.*, vol. 18, no. 5A, pp. 3579–3583, 2018.
[31] M. Tsujii, S. Kawano, S. Tsuji, H. Sawaoka, M. Hori, and R. N. DuBois, "Cyclooxygenase regulates angiogenesis induced by colon cancer cells," *Cell*, vol. 93, no. 5, pp. 705–716, 2018.
[32] X.-H. Liu *et al.*, "Upregulation of vascular endothelial growth factor by cobalt chloride-simulated hypoxia is mediated by persistent induction of cyclooxygenase-2 in a metastatic human prostate cancer cell line," *Clin. Exp. Metastasis*, vol. 17, no. 8, pp. 687–694, 2005.