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**REVIEW ARTICLE / DERLEME MAKALE**

# EVALUATING THE ROLE OF MELATONIN ON THYROID PHYSIOLOGY AND DISEASES

## *MELATONİNİN TİROİD FİZYOLOJİ VE HASTALIKLARI ÜZERİNDEKİ ROLÜNÜN DEĞERLENDİRİLMESİ*

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## ABSTRACT

**Objective:** *Melatonin (MLT) is largely produced within the pinealocytes from tryptophan, happening during the dark. MLT's binding sites have been established in numerous parts of the brain but also in the cells of the immune system, gonads, kidney, and cardiovascular system. MLT may directly or indirectly affect the thyroid gland and its activities. It can also prevent thyroid cell proliferation and interfere with thyroid hormone synthesis. The underlying mechanisms need to be carefully interpreted.*
**Result and Discussion:** *In this review the typical inhibitory effects of MLT on the thyroid gland and hormone secretion, as well as its antioxidant effects and relationship with thyroid diseases is investigated.*
**Keywords:** *Hypothyroidism, melatonin, melatonin receptors, thyroid cancer, thyroid physiology*

## ÖZ

**Amaç:** *Melatonin (MLT) büyük ölçüde triptofandan pinealositler içinde üretilir. Karanlıkta serotonin-N-asetiltransferaz aktivitesinde büyük bir artış olduğunda gerçekleşir ve serotoninin N-asetilserotonine dönüşmesine neden olur. MLT'nin bağlanma bölgeleri beynin birçok yerinde ve aynı zamanda bağışıklık sistemi, gonadlar, böbrek ve kardiyovasküler sistem hücrelerinde tespit edilmiştir. MLT, MT1 ve MT2 membran reseptörleri aracılığıyla birçok farmakolojik ve fizyolojik aktiviteyi etkiler. Ayrıca, reseptör aracılı olmayan etkileri ile antioksidan aktivite gösterir. MLT doğrudan veya dolaylı olarak tiroid bezini ve faaliyetlerini etkileyebilir. Altta yatan mekanizmaların dikkatle yorumlanması gerekmektedir.*
**Sonuç ve Tartışma:** *Bu derlemede, MLT'nin tiroid bezi ve hormon salgısı üzerindeki tipik inhibitör etkilerinin yanı sıra antioksidan etkileri ve tiroid hastalıkları ile ilişkisi incelenmiştir.*
**Anahtar Kelimeler:** *Hipotiroidizm, melatonin, melatonin reseptörleri, tiroid kanseri, tiroid fizyolojisi*

## INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT) was first isolated by Lerner and colleagues in 1958 [1]. It is an extensively distributed neurohormone being proficient of entering every cell and all subcellular sections. The melatoninergic system embraces the MLT, an indoleamine, and its molecular targets. It is secreted mainly from the pineal gland, which produces MLT during the nighttime into the

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general circulation or into the cerebrospinal fluid [2,3]. In vertebrates, MLT is synchronizing circadian rhythms, as well as sleep–wake cycle and upregulation of seasonal rhythms. Most of its activities occur via interactions with MLT receptors. Mitochondria are the chief cell organelles that form the MLT that point out that MLT is an "ancient molecule" that chiefly delivered the first cells' defense from the antioxidant species [4,5].

Besides circadian rhythm and sleep-wake cycle, MLT is effected on various biological functions such as gonadal activity, redox homeostasis, neuroprotection, immune-modulation, antioxidant and anticancer activity. Lack of MLT formation is diligently linked to the progress of aging, tumor formation, neurodegenerative diseases etc [6,7,8].

Antioxidant properties of MLT were discovered in 90's [9]. The following information of this development also recognized a MLT metabolite, cyclic-3-hydroxymelatonin (c3OHM), which is made when MLT reacts with free radicals. There have been many studies approving the capacity of MLT to directly react reactive oxygen species (ROS) [10] and to reduce oxidative mutilation to vital cellular macromolecules [11]. Studies revealed that MLT could act as an antioxidant, scavenging free radicals and avoiding cellular injury. MLT may also inhibit thyroid cell proliferation and effect on thyroid hormone production. This action was found advantageous for patients with hyperthyroidism.

Thyroid hormones play a crucial part in growth and metabolic homeostasis in mammals. In the last decade, there has been growing attention on the properties of thyroid hormones through fetal life regarding tissue differentiation and growth. Amongst the structures effected by thyroid activity, the central nervous system seems to be extremely sensitive during the developing phases [12,13]. In the blood stream MLT attaches to MT1 and MT2 receptors, and shows an important part in modifying circadian and seasonal rhythms, and also works as a free radical scavenger, an antioxidant, and an anticancer adjuvant [14]. Additionally, research has revealed that the MLT is effective on immune reactions, and an inequity of the MLT amount may cause to immunity disfunctions [15]. Due to its noticeable immunoregulatory properties, MLT has been widely explored as a potential therapeutic approach for autoimmune diseases.

The purpose of this review is to deliver some information about MLT, thyroid gland and thyroid hormones as well as to investigate the effects of MLT on the growth and activity of the thyroid gland and hyperthyroidism. The role of MLT in the pathogenesis and physiology of thyroid is also discussed.

**Melatonin Regulation**

MLT is the chief indole ring-containing hormone regulates of the sleep-wake cycle and circadian rhythm, which is a physiological cycle, takes about 25hours. This cycle is also detected in body temperature, feeding, motor activity, and sleep [16]. MLT is released into the circulation and reaches all the cells of the body, constituting the chronobiotic signal that synchronizes rhythms including circadian behavior. Changes in body temperature and locomotor activity rhythms in animal studies are detected during surgical interventions, hypoxic exposure, dietary changes, physical exercise, and numerous forms of stress [17,18]. Research presented that MLT and body temperature collectively contribute to the formation of sleep. An increase in MLT elevates fluctuations in body temperature. It was shown that MLT administration promotes reduction in locomotor activity and earlier sleep onset.

MLT studies now focus on not only sleep problems but also into a mumerous of additional possible applications as our understanding of its physiological activities grows. Aside from the neurodegenerative diseases, research involve cardiovascular disorders, cancer adjuvant treatment, side effects of conventional cancer treatments, treatment of liver diseases and injuries, fertility support, post-surgical recovery, gastrointestinal disorders, and so on [19].

Disruption of circadian rhythms is associated with higher risk of brain disorders. It was observed that chronic shift-workers are vulnerable to various diseases, including psychiatric disorders such as depression [20]. Regular physical activity helps to maintain high-amplitude circadian rhythms, particularly of clock gene expression in the SCN. It promotes their entrainment to external periodicities and improves the internal synchronization of various circadian rhythms [21].

The metabolic pathway of MLT is different in various organisms, and biosynthetic endogenous MLT acts as a molecular signal and antioxidant protection against external stress. A physiologically endogenous MLT is to emphasize the performance correlated to darkness. In mammalians the initial

step in the MLT biosynthesis pathway is the hydroxylation of L-tryptophan's indole ring by the enzyme tryptophan hydroxylase, resulting in the formation of 5-hydroxytryptophan (5-HTP). Subsequently, 5-HTP undergoes decarboxylation, facilitated by pyridoxal phosphate and the enzyme 5-hydroxytryptophan decarboxylase, yielding 5-hydroxytryptamine (5-HT). Serotonin (5-HT) is converted to MLT through the sequential action of two enzymes, serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, or AANAT) and hydroxyindole-O-methyltransferase (HIOMT). While levels of HIOMT activity remain fairly constant, the daily rhythm in MLT synthesis is generated by a concurrent rhythm in AANAT activity. (Figure 1) [22]. Animals have a single source of MLT, mitochondria. Moreover, animals cannot synthesize L-tryptophan themselves, and it must be ingested externally. Therefore, animals have lower MLT metabolism than plants.

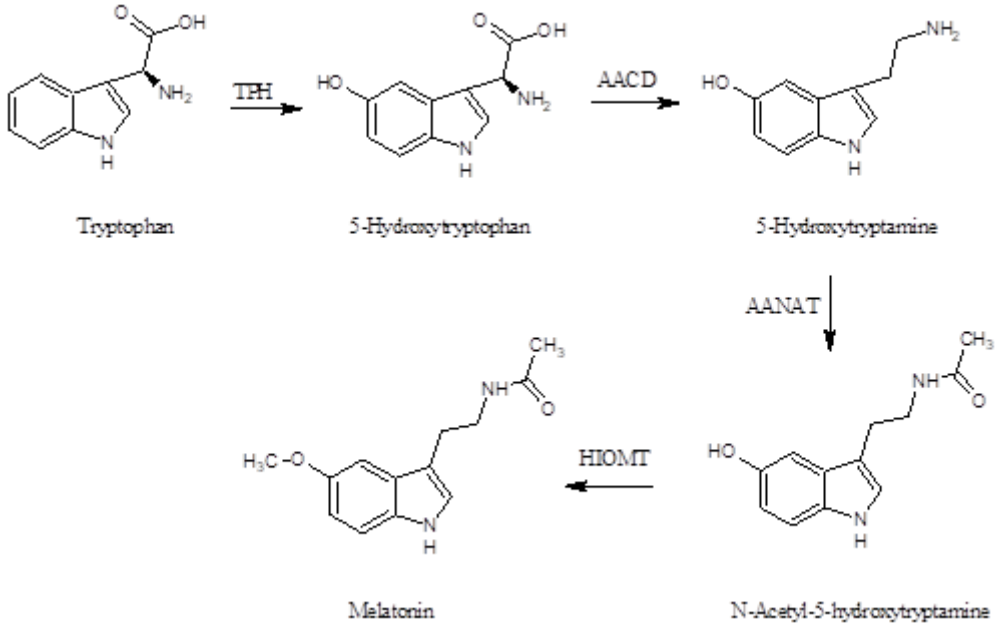


**Figure 1.** Melatonin biosynthetic pathway from tryptophan
(TPH: tryptophan hydroxylase, AACD: aromatic amino acid decarboxylase, AANAT: arylalkylamine *N*-acetyltransferase, HIOMT: hydroxylindole-O-methyltransferase)

Seasonal alterations in the biological activities of the body is controlled by MLT intermediated functions in the excretion of thyroid-stimulating hormone (TSH) and thyroid hormones. There are seasonal adjustments of TSH and thyroid hormone levels (total triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), free thyroxine (FT4) reliance on gender and age [23].

The concentration and rate of MLT synthesis reduce slowly along with the increase in age that physiopathologically associates to the development of certain neurodegenerative disorders [24]. The antioxidant properties of MLT have been related to its capacity to scavenge ROS and also the stimulus in the formation of anti-oxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX). Established on these recognized actions and pathological connection in aging-associated diseases of MLT, it is curious to enquire if the MLT administration could provide a protective effect in the aged-associated diseases [25]. MLT rises the defense of cells to the toxic actions of ionizing radiation through motivating DNA damage responses that reduce the risk of genomic instability. In addition, MLT indirectly suppresses autoimmune responses [26].

The task of the endocrine system, including several hormonal-releasing organs, undergoes ageing linked alterations that negatively influence its activity. The thyroid gland, which plays a crucial role in the human body's metabolism, growth and development, also exhibits structural and functional modifications with aging [27].

MLT triggers two high-affinity G protein-coupled receptors, MT1 and MT2, to apply useful activities in sleep and circadian abnormality, mood disorders, learning and memory, neuroprotection, drug abuse, and cancer. It was found that thyroid C-cells produce MLT under TSH regulation, also that MT1 MLT receptors are current in follicular cells and there is an indication for the contribution MLT in thyroid task by modifying the thyroglobulin gene expression in follicular cells [28].

Research have revealed that the oncostatic properties of MLT could be associated to membrane MLT receptors and nuclear RZR/ROR receptors. These activities are facilitated by the contacts of MLT with the two G-protein-coupled receptors MT1 and MT2 [29]. Other activities are proposed to be due to the free-radical-scavenging properties of this MLT. In some cancer cells, MLT interrupts the action of cell death, and inflammation. In addition, administration of MLT can lessen thyroid cancer cells [31]. MLT exhibits a significant part in the regulation of tumor formation. MT1 upregulation may inhibit some protein kinases to prevent cancer cell proliferation [29].

**Melatonin on Hypothyroidism**

Hypothyroidism is a pathological disorder of thyroid hormone insufficiency that may cause severe adverse health conditions. Hyperthyroidism due to the excess release of thyroid hormones from the thyroid gland manifests various biochemical and clinical findings. It adversely affects the cardiovascular, urogenital, and endocrine systems; electrophysiological functions; and oxidative metabolism in various organs and tissues [30].

There are two pharmacological types of hypothyroidism where the thyroid-stimulating hormone (TSH) amounts are higher than the reference and free thyroxine concentrations lower the regular range and where although the TSH amounts are higher than the reference, free thyroxine concentrations are within the normal range [32]. Hypothyroidism is 10 times more prevalent in women than in men. It is more prevalent in the elderly people, ranging from 2 to 5% of the population [33,34].

MLT is a hormone that shows a controlling role in pregnancy and thyroid physiology. Animal studies showed that, MLT is able to upregulate the estrous cycle and pregnancy [35] and converses symptoms of hypothyroidism in hypothyroid rats with the administration of exogenous MLT [36].

Thyroxin (T4) and triiodothyronine (T3) are produced from thyroid gland, both hormones escalate metabolic rate. The absence of thyroid hormone excretion could lessen body metabolism to 40–50% less than normal [37]. MLT is synthesized from the pineal gland and thyroid c-cells under TSH, therefore it can be effective in thyroid activity. The reduction of thyroid hormone concentration is defined after MLT treatment. MLT effects thyroid hormone concentrations by modulating iodothyronine-deiodinases. MLT has also a prevention activity on cell proliferation and thyroid hormone production as well as a defensive activity against oxidative injury in the thyroid gland [38,39].

Research have proposed the inhibitory action of MLT on the thyroid gland and its functions. Several procedures have been studied including short- and long-term MLT application, creation of darkness to escalate the action of the pineal gland, and pinealectomy. It was observed that MLT could directly or indirectly involve the thyroid gland activities [39,40]. Thyroid hormone is acknowledged to show chief roles in cell proliferation and differentiation, which proposes that seasonal controller of tanycyte proliferation might take part in the photoperiodic synchronization of seasonal rhythms [41].

Hypothyroidism causes to alterations in antioxidant progress [42]. MLT's antioxidative possessions and ability to defend membrane lipids, cytoplasmic proteins, and nuclear DNA. MLT facilitates most of its pharmacological activities such as the upregulation of immune activity via triggering of G-protein coupled MT1 and MT2 cell surface receptors. Additionally, MLT receptors are also placed on several tissues involving the thyroid follicular and parafollicular cells. In an animal study MLT administration of hypothyroid mice increase the thyroid hormones through modifying the neuroendocrine axis and control of hypophyseal TSH. It was observed that MLT indifferently modified the MT1 and MT2 receptor protein expression in the pituitary and thyroid gland. It could be that MLT controls the hypophyseal-thyroid activity in hypothyroid mice via different initiation of MT1 and MT2 receptors in the pituitary and thyroid gland [43].

Graves' disease (GD) and Hashimoto's thyroiditis (HT) are two life-threatening autoimmune thyroid disease (AITD). Thyroid T-lymphocytes are firstly stimulated against a thyroid autoantigen, then stimulation of B cell- or cytotoxic T cell-driven immunity occurs [44]. MLT exerts

immunomodulatory possessions and existing in the thyroid gland. It was established that the single-nucleotide polymorphism of MTNR1A, coding the MT1 protein, was linked with a susceptibility to GD and thyroid autoantibody creation, which supports the idea that the MLT may effect the happening of AITD and clinical features. It is known that MLT treatment elevates plasma thyroid hormone concentrations and enhances thyrocyte destruction and the T-cell proliferation capacity in a TG-immunized thyroiditis mouse model [32].

**Thyroid, Ovarian Disorders and Melatonin**

Thyroid hormones have been identified in the rat embryos during the second week of growth and in the human fetus before the beginning of functions of the fetal thyroid gland [45]. Thyroid dysfunctions, which are more widespread among females, may inhibit reproduction and fertility. Severe thyroid malfunction could cause menstrual syndromes and infertility through direct and indirect relations with the hypothalamo-pituitary-ovarian axis and the reproductive organs. Nonetheless, the precise occurrence of infertility in women with thyroid dysfunction remains unclear [46]. There is a growing indication for thyroid dysfunctions generally arising in women with ovarian disorders. For this reason, thyroid dysfunctions could be one of the causes of female infertility. Irregular thyroid-stimulating hormone (TSH) concentrations are stated in 6.3% of anovulatory infertile women and there is an indication signifying the connotation of hyperthyroidism with amenorrhea, and hypothyroidism with oligomenorrhea, diminished libido, and anovulation [47]. Accordingly, both hypo- and hyperthyroidism might influence the metabolism of estrogens and androgens eventually halting ovulation [48].

Investigation of the activity of MLT and L-thyroxine (T4) on the expression of several receptors, and some metabolic, reproductive, and gonadotropic hormones in polycystic ovary syndrome (PCOS) in an animal study showed a noteworthy increase in thyroid follicle numbers. MLT and T4 management of PCOS rats occasioned in an important reduction in the circulating amount of T3 and T4 [48].

It is known that one of the reasons of infertility is circadian rhythm conditions. Clock 3111 T/C and Period3 VNTR gene polymorphisms and circadian rhythm hormones in infertile women was investigated. The results revealed that the clock protein concentration of the infertile group was greater than the fertile group. MLT concentration of the fertile group was clearly associated with progesterone amounts and negatively connected with cortisol amounts. Additionally, MLT concentrations of the infertile group were completely related with LH amountss and negatively connected with cortisol amounts [49].

MLT stops lessening of ovarian and thyroid mass, number of pups, follicular diameter and thyroid epithelial proportion of the matrices with hypothyroidism. Animal studies showed that rats without induced hypothyroidism presented less body weight gain, gonad and thyroid weight, and gonad cell proliferation index. MLT inhibits effects of maternal hypothyroidism on the offspring of rats [50]. MLT also assistances to uphold neuronal activity in hypothyroid newborn rats by preventing apoptosis and supporting survival. This highlight the importance of MLT use by the mother in hypothyroid condition during gestation and lactation to preserve the reliability of motor neurons in the newborns [51].

Disorder of the circadian rhythm involving sleeping problems, wakefulness and hormone secretion disorders play an important part in infertility. It was observed that insomnia consequences in lessened MLT production. In females low MLT levels are connected with greater formation of free oxygen radicals (ROS), and therefore poorer quality of oocytes. MLT administration escalates its efficacy by improving the quality of oocytes, rise the percentage of fertilization and the quality of the developing embryos [52]. MLT seems to be a crucial indoleamine associated to female fertility. Its elevated plasma levels have been found in women with infertility due to hypothalamus disorder. MLT is connected not only with fertility, but also with the development of pregnancy. An escalation in MLT amounts during pregnancy and its rapid drop soon after pregnancy ended have been exposed [53].

**Melatonin and Thyroid Cancer**

The thyroid is an essential endocrine gland situated at the base of the throat anterior to the trachea. The thyroid uses iodine to synthesize hormones that regulate the heart rate, blood pressure, body temperature, and basal metabolic rate. Thyroid cancers are classified as differentiated thyroid cancers

(DTC) which includes papillary, follicular, medullary, and undifferentiated or anaplastic thyroid cancers (ATC). Thyroid cancer happens more often in women than in men, at an estimated ratio of 3:1. It can be seen in any age-group however more so in adults aged 45 to 54 years [54].

Research have established that MLT lessens the pathogenesis of cancer by directly disturbing carcinogenesis and indirectly distracting the circadian cycle. MLT is nontoxic and displays a variety of advantageous properties against cancer through apoptotic, antiangiogenic, antiproliferative, and metastasis-inhibitory pathways [55]. Remarkably, MLT has presented some synergistic activities with ionizing radiation and chemotherapy, which is separate from classical antioxidant compounds that are commonly administered for the lessening of adverse effects of radiotherapy and chemotherapy [26].

Thyroid carcinoma is the most common endocrine malignancy with growing frequency worldwide, so explains the common of deaths from endocrine cancers [56]. MLT has enhanced or induced apoptosis in many different cancer cells. MLT is a powerful antioxidant agent that defends against the toxic effects of radiation and chemotherapy. Additionally, in some cancer cells, MLT assistances alerting cancer cells to healing [31].

MLT and its metabolites have extremely broad antioxidant actions, including the ability to neutralize superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), single oxygen ($^1O_2$), hydrogen peroxide ($H_2O_2$), hypochlorous acid (HOCl), nitric oxide (NO), and peroxynitrite anions ($ONOO^-$) [57]. In addition to these well-described actions, melatonin also reportedly chelates transition metals, which are involved in the Fenton/Haber–Weiss reactions; in doing so, melatonin reduces the formation of the devastatingly toxic hydroxyl radical resulting in the reduction of oxidative stress. Furthermore, MLT can increase the expression of antioxidant enzymes (SOD, CAT, and GPx) and scavenge free radicals [58]. Therefore, MLT is proposed to have a potent antioxidant capability and protective properties against oxidative stress [59]. Unlike most small-molecule biological antioxidants such as vitamin C, α-tocopherol and lipoic acid, MLT does not redox-cycle. It undergoes molecular rearrangement, effectively removing the free electron from the system – a so-called suicidal antioxidant [60]. MLT prevents lipid peroxidation by capturing the peroxide radical unlike antioxidants, such as ascorbic acid, alpha-tocopherol, and GSH. It has been revealed that liver, kidney, and brain tissue glutathione peroxidase activity in animal experiments elevated after the administration of MLT. Significant decreases in liver, lung, brain tissue, and glutathione peroxidase activity were reported in rats for which pinealectomy is made [61].

In a study, it was observed that MLT considerably reduced anaplastic thyroid carcinoma (ATC) cells and augmented LDH activity in ATC cells [62]. Investigation of the radioprotective properties of MLT against thyroid gland injury in rats showed that MLT administration before radiotherapy lessened thyroid gland damage caused by irradiation [63]. Papillary thyroid carcinoma (PTC) is the most common subtype of malignant thyroid nodule, and a significant increase in the number of thyroid cancer cases has been attributed to the increase in the incidence of PTC. It was found that, the level of MLT is clearly decreased in PTC, suggesting a potential role for MLT in the treatment of malignant thyroid tumors. [64]. Studies show a protective role for MLT against thyroid oxidative damage caused by carcinogens in thyroid cancer. MLT could be an effective agent in preventing oxidative damage and potentially reducing the risk of thyroid cancer formation caused by iodine compounds used in iodine prophylaxis [65]. Furthermore It was showed that MLT administered before radiotherapy provided significant protective effect against acute rat thyroid gland dysfunction caused by single dose radiotherapy [63].

Research revealed that not only iodine insufficiency, but also its additional presence could be related to thyroid cancer. Potassium iodate (KIO3), which is mostly used in salt iodization, may escalate oxidative damage to membrane lipids. MLT is a strong antioxidant, which defends against lipid peroxidation (LPO) in the thyroid [66]. Showed the defensive effects of MLT in the maximum possible *in vitro* application, against KIO3-induced oxidative damage in several tissues including thyroid. MLT lowered LPO in the thyroid and effective defending action was detected. It was concluded that MLT could be thought to escape the possible harmful effects of iodine derivatives administered in iodine prophylaxis. They also revealed that defending properties of MLT together with indole-3-propionic acid (I3P) were much stronger than those exposed by each molecule used independently. MLT and I3P employ cumulative defensive properties against oxidative damage caused by KIO3 [67]. Studies showed that MLT lessens LPO in various tissues and this defensive action not depend on iron level. This backs

the declaration that MLT is a unique antioxidant, which does not affect biological progressions, whereas it is active under circumstances with additional oxidative stress [78].

Current research showed that a small rise in thyroid cancer mortality was observed in the last two decades [68]. Increasing indication has proposed that circadian disorder is a possible risk factor for thyroid cancer [69]. It was found that extreme insomnia indications were related to a developed thyroid cancer risk in postmenopausal women [70] backup a part of sleep deficits and circadian dysfunction in thyroid cancer growth. Furthermore, a study established that circadian clock gene expression patterns were different in thyroid carcinoma tissue samples than in normal thyroid [71,72].

Dabrafenib has presented potent anticancer actions in patients with thyroid cancer. To prevent the resistance of thyroid cancer cells to dabrafenib, it was used with MLT as a combination on the proliferation, cell cycle arrest, apoptosis, migration and invasion of anaplastic thyroid cancer cells. MLT improved dabrafenib-mediated inhibition of cell proliferation, migration and invasion, and stimulated dabrafenib-induced apoptosis and cell cycle arrest in anaplastic thyroid cancer cells. The outcomes established that MLT synergized the anticancer activity of dabrafenib and delivered new approach for the treatment of anaplastic thyroid cancer [73].

It has been revealed that MLT may increase the effectiveness of anticancer drugs and directly prevent tumorigenesis. Furthermore, while MLT characteristically displays anti-apoptotic activities in normal cells, it shows pro-apoptotic activity in cancer cells. In a study the MDA-T41 thyroid cancer cell line was cultured with changing concentrations of MLT. The outcomes displayed that MLT delivered anti-apoptotic effects to MDA-T41 cells [74].

## RESULT AND DISCUSSION

During the last decade, investigations were focused on MLT. It has been recognized not only in the pineal gland, but also in extrapineal tissues. MLT has an exceptional situation between the neurohormones. Research and clinical studies display the direct contribution and dynamic activity of MLT in the pathogenesis of many diseases such as cancer, immune diseases, neurodegenerative conditions, radiation disorders, etc. It was observed that MLT activity could be beneficial for the improvement of the management of numerous diseases.

Since MLT could inhibit thyroid cell proliferation and effect on thyroid hormone synthesis, this properties might be advantageous for hyperthyroidism patients. Earliest studies revealed that MLT treatment improved the triggering effect of TSH on thyroxin secretion. MLT activity is dose-dependent. High doses inhibited thyroid gland reaction to TSH. The control of the female reproductive system is one of the most related activities of thyroid hormones. Sufficient thyroid hormones synthesis is crucial for menstrual task and fertility as well as for the effective maintenance of pregnancy. The association between reproductive dysfunction and thyroid disorders is predominantly significant and draws consideration worldwide.

There are studies indicating a certain connection between MLT and thyroid action. It was proposed that there is a paracrine act for MLT in the regulation of thyroid action. Treatment of MLT is favorable as an antioxidant in thyroid tissues under circumstances of augmented OS, and could be supportive to decrease the oxidative developments involved in thyroid diseases.

### Conclusion

MLT is an endogen hormone mainly produced in the pineal gland in response to darkness. Besides from regulating our body’s internal clock, it possesses strong antioxidant properties. MLT reveals promise in preventing and treating various health issues, such as cancer. Melatonin itself has a positive effect on thyroid function. It also affects sleep, general health, and many other relevant symptoms. Within the thyroid gland, thyroid hormone synthesis is mainly regulated by the thyroid-stimulating hormone (TSH). To date, there is data in literature pointing to the relationship between MLT and thyroid activity. There is also reasearch showing MLT activities on the thyroid gland itself, such as the inhibitory effect of MLT on cell proliferation and thyroid hormone synthesis. By supporting the pineal gland, there is also evidence that it can help enhance the body's ability to convert T4 into T3, a key issue for patients with hypothyroidism. The thyroid gland is characterized by a high level of oxidative stress, and the use

of pro-oxidants can lead to miscellaneous damage and diseases of this delicate papillon gland. Research shows that MLT may act as an antioxidant, rounding up excess free radicals and preventing cellular damage. MLT may also prevent thyroid cell proliferation and interfere with thyroid hormone synthesis. This effect may be beneficial for people with hyperthyroidism. Still, it may be problematic for people with normal thyroid function and certainly hypothyroidism. For this reason, people who take MLT regularly may need to check their thyroid levels to be sure they are optimal.

Taken together, MLT potentiates radiation-induced cytotoxicity in thyroid cancer cells via inhibition of NF-κB/p65 phosphorylation and ROS induction. MLT enhances sensitivity of thyroid cancer cells to irradiation *in vitro*. It has been experimentally proven that the MLT molecule has lethal effects on thyroid cancer cells and can be used in the protection of thyroid cancer [75]. It can be concluded that the use of MLT may have beneficial effects on preventing or reducing some thyroid related diseases.

However, the fact that MLT has not yet been approved by the FDA is a factor that limits its clinical use. MLT products are considered dietary supplements.

## AUTHOR CONTRIBUTIONS

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## CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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