Review Article: Effect of Medicinal Herbs in the Treatment of Thyroid Malignancy

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ABSTRACT

Thyroid cancer is the most common endocrine malignant tumor, and its incidence is on the rise. A survey conducted by the Iranian Cancer Institute showed that thyroid cancer constitutes 1.8% of all cancers and 76.1% of endocrine cancers. A lot of studies are being conducted in order to prevent, alleviate pain, and treat cancer using medicinal herbs. Medicinal herbs are important sources of, and rich in, natural antioxidants. There is lots of evidence that some herbal compounds such as vitamins, flavonoids, polyphenols, carotenoids, and herbal steroids have anticancer properties and can act as mutagenic inhibitors. In this review article, first, prevalence and characteristics of thyroid cancer will be examined. Then, a variety of compounds contained in the plant extracts, which have anticancer properties, and methods of extracting plant extracts will be investigated. Moreover, a number of studies which investigated the impact of medicinal herbs on the thyroid malignancy will be reviewed.

1. Introduction

Thyroid gland disorder is among the most prevalent endocrine diseases, because numerous conditions and components may intervene in the biosynthesis and metabolism of thyroid hormones [1]. Thyroid cancer is the most frequent endocrine malignant tumor [2] and constitutes 1% of all malignant diseases, which is still on the rise [3]. Deaths caused by the head and neck cancers have decreased in the United States of America (USA), except for thyroid cancer that remains constant. According to the research findings, thyroid cancer incidence has increased in all sizes and both genders from 1988 to 2005. Thyroid cancer is the main cause of death due to endocrine malignancies and

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constitutes 1% of all malignancies in Western countries and 2% of the total fatal cancers [4].

Thyroid cancer constitutes more than 95% of endocrine cancers in the USA. More than 200000 people suffer from this type of cancer in the USA, while a number of these patients do not respond to conventional treatments [4]. Meanwhile, approximately 2000 patients suffering from thyroid cancer lose their lives each year, and unfortunately, it is still on the rise. Despite the decrease in overall mortality due to cancer in the USA, the incidence of thyroid cancer doubled in the last decade and increased up to 75% in the past 5 years [5].

Thyroid cancer is also on the rise in Iran. A survey conducted by the Iranian Cancer Institute reported that thyroid cancer constitutes 1.8% of all cancers and 76.1% of endocrine cancers [6]. In Iran, the incidence rate of this disease in women and men in 2005 were 2.02 and 0.82, respectively, and in 2009, it increased to 4.2 and 1.36, respectively. The mean age of such patients was approximately 43 years in Iran [7]. Additionally, women's incidence rate is 3 times higher than that of men in Iran [7].

Papillary thyroid carcinoma is the most prevalent type of thyroid cancer and constitutes 80% of thyroid cancers. The incidence rate of this type of cancer in women is more than men, and most patients are middle-aged (30 to 60 years old). This type of cancer is often more aggressive in older people. This tumor, which often contains follicular cells in one-third of cases, spreads through the lymph to lymph nodes and may also lead to the lung metastases [3, 4]. Diet containing iodine highly influences the prevalence of this type of cancer and, in some cases, papillary cancer morphology [3].

Follicular cancer consists of about 20% of different types of thyroid cancers and has the higher risk of metastasis and recurrence, with higher prevalence in areas where people suffer from iodine deficiency [3]. Less than 5% of the cells within the thyroid gland are C cells which lead to medullary thyroid carcinoma. Medullary carcinoma constitutes 3% of thyroid cancers [3]. Anaplastic Thyroid Cancer (ATC) is the most malignant type of thyroid cancer and more prevalent in the elderly. Anaplastic cancer is rare and constitutes almost 2% of thyroid cancers. This type of cancer leads to quick metastasis, and treatment with radioactive iodine is not possible. In fact, an effective treatment does not exist for this type of cancer; this disease is generally fatal, and about 80% of patients lose their lives within a year after the diagnosis [3].

2. Medicinal Herbs

Nature is rich in medicinal compounds, a portion of which lies in the plants. From thousands of years ago, herbs had a lot of applications as traditional medicines. Recently, due to the side effects of the synthetic medications, the use of herbal medicines in the treatment of a variety of diseases and the use of natural antioxidants in food production attracted a great attention in the industrial and developing countries. In the field of extracting biological compounds from plants, research is quickly being performed [8].

Consuming different types of fruits and vegetables leads to a reduced risk of cancer. For a long time, medicinal herbs have been used by local people in various parts of the world including the USA, China, India, Mexico, Morocco, Saudi Arabia, Taiwan, and so on [9]. There are more than 20000 species of plants used as traditional medicine [8]. Over 3000 plants with anticancer properties are identified throughout the world [10]. Based on studies, more than 30% of cancer patients use herbal extracts for treatment [11, 12].

Numerous studies have been conducted to prevent diseases, alleviate pain, and treat cancer using medicinal plants. In Asia, about 40-62% of cancer patients tend to use traditional Asian herbs for treatment [13, 14]. Herbal remedies often have less toxicity and side effects, compared to other treatment methods. Also, this medicine is less invasive and cost-effective. Anticancer medications such as irinotecan, vincristine, and etoposide are extracted from plants [15].

Therefore, it is hoped that conducting more research on extracting herbal medicine from medicinal plants leads to the development of modern and effective medications for cancer treatment. Medicinal plants are important rich sources of natural antioxidants. Extensive evidence suggests that some herbal compounds such as vitamins, carotenoids, polyphenols, flavonoids, and plant steroids can function as mutagenic inhibitors.

3. Phenolic and Flavonoid Compounds

Polyphenols which abound in vegetables and fruits have antiradical, anticancer, anti-inflammatory, antiviral, and antimicrobial activities [16]. Phenolic compounds found in plants function as strong antioxidants. Antioxidant activity in different plants is considered among the important reasons for creating cell toxicity and apoptosis induction in cancer cells [17]. By sweeping through the free radicals and by increasing the host's defense system

of antioxidant, phenolic compounds have some reported protective effects against the disruptive side effects of genotoxic cancer producers [16, 18].

Studies on the effect of various herbs extracts on the different categories of cancer cells recognized flavonoids and phenolic compounds in plants as the important anticancer properties [18-20]. Various studies have argued that the anticancer effects of polyphenol compounds function through mechanisms such as the induction of programmed cell death, the inhibition of kinase proteins activities, the prevention of cells invasion, and cell growth inhibition [21]. Food flavonoids are plant pigments that exist in fruits, seeds, nuts, wine, tea, and so on. A normal diet must contain 2 gr of flavonoids per day [22, 23].

Flavonoids are the most abundant antioxidant compounds in the majority of medicinal herbs that have antiproliferative and anticancer effects through the induction of apoptosis and inhibition of proliferation in cells. According to studies, flavonoids' anticancer properties function through the inhibition of polymerization of tubulins, the inhibition of destructive effects of the free radicals, and the induction of apoptosis [21, 24].

Quercetin

Quercetin (3, 30, 40, 5, 7-pentahydroxyflavone) is the most abundant flavonoid, available in various fruits and vegetables [25]. In addition, quercetin, as a dietary supplement, has antioxidant, antiproliferative, and anti-inflammatory properties. Several studies have indicated that quercetin like other flavonoids has many other therapeutic properties such as the induction of apoptosis in tumor cells, antiviral, antioxidant, anti-inflammatory properties, and antiproliferative activity [26, 27].

Quercetin also has antithyroid and goitrogenic effects [28]. Resveratrol is a natural polyphenol found in grapes and berries, with antiproliferative, antioxidant, and, anti-inflammatory properties [29]. Therefore, it is used as a dietary supplement. Resveratrol is a compound with antioxidant, anti-inflammatory, and apoptotic properties. It can significantly help to protect the heart and prevent diabetes and cancer [29].

Curcumin

Curcumin has anti-inflammatory properties and is a great antioxidant produced by some plants. Curcumin is a curcuminoid with natural pigments and strong antioxidant, anti-inflammatory, antiproliferative, and pro-apoptotic properties [30-32]. The mechanisms by which curcumin inhibits the tumor include the combination of antioxidant, anti-inflammatory, anti-angiogenesis, anti-metastasis, cell cycle inhibition, and proapoptotic properties which induce their inhibitory effects on cancer induction through the regulation of genes and molecules involved in this route [33].

Alkaloids

Alkaloids, like beta-carbolines, have anticancer effects shown in several cancer cells [34]. Alkaloids such as harmines and beta-carbolines influence the prevention of cancer cell growth through apoptosis, replication disorders, and angiogenesis inhibition [35-38].

Fatty acids such as linoleic acid

Oil-bearing crops of many plants contain fatty acids, particularly linoleic acid. Essential fatty acids and their metabolites prevent tumor growth by limiting the production of free radicals in tumor cells. Linoleic acid causes the formation of peroxidase lipid and the induction of apoptosis. Studies have suggested that omega-6 fatty acids can slow down the growth of cancerous cells in the lungs (in limited concentration). In high concentrations, it stimulates apoptosis in colorectal cancer and has a toxic effect on the tumor cells. Linoleic acid protects the body by creating changes in the potential of mitochondria membrane and by creating active oxygen radicals, which eventually leads to releasing C cytochrome and the activation of caspase-3 and -9 and stimulates apoptosis, accordingly [39].

Phytosterols

Studies revealed that diets comprising high amounts of vegetables and herbs containing phytosterols decrease colorectal cancer [40]. Phytosterols or plant sterols have a structure similar to cholesterol. One of the most common phytosterols is beta-sitosterol, which has very strong anticancer properties. Foods containing phytosterols protect the body against various cancers such as colorectal, breast, and prostate cancers. One of the important mechanisms of phytosterols, as well as their effect on cancer cells is through the induction of apoptosis [41].

Phytoestrogens

Phytoestrogens are also active bio-compounds. They have different structures, but their main feature is the existence of the phenyl ring which is necessary in connecting to the estrogen receptor. Performance mechanism of

phytoestrogens in the prevention of breast cancer is by virtue of their similarity to estradiol in terms of chemical structure. This similarity helps them connect to estrogen receptors. In addition, they function as antioxidants and protect the body from the damaging effects of free radicals. Also, they have an antiproliferative impact on cancer cells and prevent the growth of tumors.

A combination of phytoestrogens called genistein has a preventive effect on tyrosine kinase [42] and topoisomerase [43, 44]. Therefore, they block signals of cell growth by interfering in a message transfer path [43, 44]. This signal increases the expression of proto-oncogenes such as C-Jun, C-Fos, C-Myc, by which phytoestrogens interact. Phytoestrogens prevent the sulfotransferase enzyme (enzymes involved in the activation of pre-carcinogen food compounds). As noted earlier, phytoestrogens connect to the receptor of estrogens, function as weak estrogens and decrease the risk of breast cancer.

Sometimes, phytoestrogens compete with innate and inner estrogens to connect to the receptor. When inner estrogen levels are low, phytoestrogens play the role of estrogens and connect to the receptor. However, phytoestrogens in high rates occupy the receptor and function as anti-estrogen and prevent breast cancer [46].

Cucurbitacin E

Cucurbitacin E or Cu E or Alpha-alatarin with the molecular formula of C32H99O8, is a four-ring triterpenoid, extracted from plants, especially the family Cucurbitaceae. Cucurbitacin E prevents cancer by inhibiting the function of phosphorile STAT3 and JAK2 proteins and impacting downstream genes. STAT3 protein connects to Bcl-xl, CyclinD1, and VEGFR2 and activates them. Thus, Cucurbitacin E suppresses the expression of these genes. Bcl-xl, an anti-apoptotic factor, is the main protein disabled by STAT [47, 48].

Beta-carotene

Beta-carotene as a precursor of vitamin A is a biological pigment soluble in membrane fat, and protects cell membranes and cells from the effects of free radicals. Carotenoids help the normal functioning of the connexin-46 genes, and they keep cells sensitive; consequently, they help prevent irregular and uncontrolled cell growth [49].

4. Methods of Extracting Herbal Extracts

Extracting plants' beneficial ingredients is performed by various methods in the treatment of diseases. At the pre-extraction stage, plant samples are collected, dried, and milled. These steps are important in extracting phytochemicals from medicinal plants [50]. In air drying method, the different parts of medicinal plants are dried by being exposed to the air until the moisture disappears. Depending on the part of the plant, the time for drying may range from three days to one month [50].

In microwave drying method, electromagnetic waves are used to produce heat and dry the different parts of plants. This method is much faster, compared to the air drying technique; however, in some cases, it may cause changes in the structure of phytochemicals [51]. In the freeze drying method, first, the medicinal herb is frozen, then, liquid inside the plant is evaporated through sublimation. This method is costlier, compared to the other ones; however, it is appropriate for heat-sensitive plants [50]. The oven drying method is also a simple and fast approach of drying herbs [52].

In the extraction stage by a proper solvent, the effective compounds of the plant are extracted. In the maceration method, dried plant specimens are soaked inside a container containing appropriate solvent for at least three days at room temperature. After the plant's phytochemicals disappear, the mixture is filtered. This is a simple and widely used method in extracting medicinal plants [50]. In the Soxhlet method, desired samples are placed within a porous container. Right at the bottom of the container, a proper solvent is heated and its vapors cross through the sample container and after becoming recongested, they reform as drops. This method is widely used, however, it is slow technique for extracting herbs [53].

The Microwave Assisted Extraction (MAE) is a newer and faster method for the extraction of herbal compounds, performed by the waves based on microwave energy absorption by the polar molecules of chemical compounds. Generally, in this method, high temperature and pressure lead to the easier and faster extraction of plants' compounds. Reduced use of solvents and shorter extraction time are its advantages; restriction in the extraction of small phenolic compounds like phenolic acids is the disadvantage of this method [51]. In Ultrasound-Assisted Extraction (UAE) method where ultrasound waves with the wavelength of 20 KH to 2000 KH are used, highly energetic waves destruct the cell membrane of plant, and its permeability increases; thus, phytochemicals can be easily extracted from the plant into the solvent [54].

5. Studies Conducted on the Influence of Medicinal Herbs on Thyroid Malignancy

Beate Rinner et al. investigated 8 lines of the medullary thyroid carcinoma cell by 10 factors of species of Stemona (Stemonaceae), Aglaia (Meliaceae), and Artemisia (Asteraceae). They evaluated the effects of these plants on the rate of apoptosis and proliferation [55]. Extracts of these plants are used in Chinese traditional medicine. Medullary Thyroid Carcinoma (MTC) is rare tumor producing calcitonin resulted from the parafollicular cells of thyroid C cells. MTC is relatively insensitive to conventional chemotherapy and radiation therapy, and the only therapeutic option for this cancer is surgery [56].

According to the results of this study, a strong antiproliferative effect of the extracts of Aglaia species and Artesunate were identified; while, Stemona tuberosa Lour showed an apoptotic effect. Beate Rinner stated that the activity of new herbal extracts probably provides a new approach to the successful treatment of medullary thyroid carcinoma, resistant to chemotherapy [55]. A large number of studies suggested that isoflavones may alter the function of endocrine glands and can reduce the level of thyroid hormone. In addition, flavonoids inhibit the cell growth in thyroid tumors; however, flavonoids can reduce radioactive absorption, which, in turn, may decrease the effectiveness of radiotherapy [23].

In a study, HTH7 and KAT18 cells derived from patients suffering from ATC were analyzed by the different doses of chrysin (25-50 mm). The results indicated that chrysin inhibits the growth of ATC cells through apoptosis in vitro. Therefore, the natural flavonoid chrysin can probably be considered as a new medication for the treatment of ATC [57].

In a study, the effects of some flavonoids such as genistein, apigenin, luteolin, chrysin, kaempferol, and biochanin were studied on the thyroid carcinoma cells of humans, UCLANPA-87-1 (NPA) (papillary carcinoma), UCLA RO-82W-1 (WRO) (follicular carcinoma), and UCLA RO-81A-1 (anaplastic carcinoma). The results suggested that among investigated flavonoids, luteolin and apigenin are strong inhibitors of human's thyroid carcinoma cells, and flavonoids may provide a new class of therapeutic agents in the management of thyroid cancer [58]. In addition to the creation of apoptosis in thyroid cancer cells, experimental data indicated that flavonoids can also interfere with thyroid hormones [1].

Findings revealed that soy consumption by humans temporarily increases TSH levels with a significant correlation between the basal levels of daidzein and thyrotropin [59]. Bitto et al. argued that the intake of genistein which is an isoflavone existing in soy foods, by postmenopausal women for 36 months did not significantly affect their thyroid function [60]. The same results were obtained by Bruce et al. where postmenopausal women used isoflavones from soya for 6 months on a daily basis [61].

Ishizuki et al. investigated the daily consumption of 30 gr of soy for one to three months; they observed some of the symptoms of hypometabolic and goiter in half of the people who had consumed the amount for three months. However, one month after discontinuing the intake of soy, the symptoms disappeared. The authors suggested that the excessive intake of soy, depending on the duration of consumption, may cause goiter in healthy people [62]. In dogs, the consumption of soy phytoestrogens for 12 months increased the level of T4 serum; while the level of T3 serum remained unchanged. The authors suggested that this effect could be due to the inhibition of 50-deiodinases activity [63].

The repressive effect of some flavonoids on thyroid function is clearer in rats. Chandra et al. reported that catechin inhibits the activity of thyroperoxidase and reduces the serum levels of T3 and T4 and increases TSH concentration [64]. Chandra et al. also argued that the extracts of green and black tea change the physiology and structure of thyroid gland and lead to the enlargement, and the hypertrophy or hyperplasia of thyroid gland [65].

Several studies have suggested that flavonoids, including quercetin can impair thyroid function. One study reported that quercetin inhibits the growth of thyroid cells and iodine uptake [25]. The rate of daily consumption of quercetin differs in societies. The average daily consumption of quercetin is reported to be between 20 and 40 mg; though, its consumption rate is reported to be up to 500 mg in people who highly consume apples, onions, and tomatoes [25].

Cesidio Giuliani et al. investigated the effects of quercetin on the expression of other thyroid-limiting genes. They concluded that quercetin reduces the expression of thyrotropin receptor, thyroid peroxidase and thyroglobulin genes. Moreover, they revealed that quercetin has preventive effects on thyroid function and disrupts thyroid function; it is recommended to take the necessary precautions when using it as a dietary supplement or for therapeutic use [66].

A study explored the effects of resveratrol on the absorption of sodium/iodide symporter expression and iodide uptake in thyrocyte after prolonged treatment. It was reported that resveratrol reduces sodium/iodide symporter expression and iodide uptake in thyrocyte. In addition, the preventive effect of resveratrol on iodide absorption was confirmed in Sprague-Dawley rats in vivo. This study argued that the long-term treatment of resveratrol inhibits gene expression, symporter expression, iodide uptake, and thyroid function. This information suggests that resveratrol can disrupt the thyroid, which reflects the need to be cautious when using it as a supplement and for therapeutic goals [29].

Cesidio Giuliani et al. investigated the additional expression of thyroid-specific genes, including thyroglobulin, thyroid peroxidase, TSH receptor, Nkx2-1, Foxe1, and Pax8 in FRTL-5 thyroid rat cell line. According to the results of this study, a reduction was observed in the expression of these genes in FRTL-5 cells under the treatment with 10 micrometers of resveratrol. Clinical signs of hypothyroid were not observed in rats, a significant increase in the size of their thyroid was observed. The levels of TSH serum and thyroid hormone were normal. Histological and immunohistochemical analysis demonstrated an increase in the proliferative activity of their thyroid, while being treated using resveratrol.

This information suggests that resveratrol disturbs the thyroid, and the necessary care should be applied when using it as a supplement or for treatment goals [67]. L.H Duntas (2011) reported the antioxidant, anti-inflammatory, and apoptotic properties of resveratrol [29]. L.H. Duntas also stated that among various tumors, resveratrol may prevent the cell growth both in the papillary thyroid carcinoma and thyroid follicular cancer, through the activation of Mitogen-Activated Protein Kinase (MAPK) signal transduction pathway, as well as the increase of p53 and its phosphorization.

Finally, by the increased trapping of iodide by thyroid cells, resveratrol influences thyroid function, and with increased TSH secretion via activation of sirtuins and the phosphatidylinositol-4-phosphate 5 kinase γ (PIP5Kγ) pathway, it may negatively impact the thyroid metabolism [29].

In a randomized double-blind study with placebo and control groups, the effect of a daily supplement containing 90 mg of isoflavones (aglycone weight), compared to placebo was studied in 38 postmenopausal women after the age of 64-83 years not receiving hormone replacement therapy. According to their results, the isoflavones existing in soy had no positive effect on the thyroid function [61].

Catechins are flavonoids which abound in green tea. Flavonoids have anti-thyroid effects. Amar K. Chandra et al. explored the effects of high doses of green tea on thyroid physiology. The green tea extract was orally fed to male albino rats for 30 days in different doses. Similarly, different doses of pure catechins were fed to the same rats. Increase in the doses of green tea in the catechins-treated groups led to an increase in body weight along with hypertrophy and thyroid follicular hyperplasia.

The activity of thyroid peroxidase and 50-deiodinase decreased, and Na^+/K^+-ATPase thyroidal activity increased. In addition, the decline in T3 and T4 serum levels and a significant increase in TSH serum level were observed. According to the results, catechins and green tea extract may have an anti-thyroid property. Moreover, probably the consumption a high dose of green tea can lead to reduced thyroid function [64].

In a randomized double-blind study with placebo and control groups, 389 osteopenic, postmenopausal women were studied for 24 months. Participants received 54 mg of genistein aglycone daily along with calcium and vitamin D3 in therapeutic doses. The data suggested that the consumption of genistein aglycone of <54 mg doses in deciliter does not significantly increase the risk of clinical hypothyroid [60]. The results of a number of studies

Table 1. Results of a number of studies on the impact of various plants on the thyroid function

Results	Protocols	Extracts/ Materials	Disease/Cells/Animals	Authors
Antiproliferative and apoptosis effects	1- Casy-1-Cell Counter & Analyzer 2- WST-1 - based cytotoxicity assay 3- DAPI Staining (by the measurement of caspase-3 activity and Bcl-2 Expression)	Ten agents from the plants of genera Stemona (Stemonaceae), Aglaia (Meliaceae) and Artemisia (Asteraceae)	Eight cell lines from Medullary Thyroid Carcinoma (MTC)	Beate Rinner et al. (2004) [55]

Results	Protocols	Extracts/ Materials	Disease/Cells/Animals	Authors
Decreased the RNA expression of the thyroid-restricted NIS, TSHR, TPO and TG genes/ decrease in TG gene expression/ decreased the radioiodine uptake in rats.	1- RNA isolation and Northern analysis 2- Western blot 3- TSH and thyroid hormones determination by ELISA Kit 4- BCA protein assays kits	Quercetin (one type of flavonoids)	F1 subclone of FRTL-5 rat thyroid cell/ male adult Sprague–Dawley rats	Cesidio Giuliani et al. (2014) [25]
Decreased the sodium/ iodide symporter RNA and protein expression (as a function of time)/ decreased cellular iodide uptake after 48 h/ inhibitory effect of resveratrol on iodide uptake.	1- RNA isolation and Northern analysis 2- Western blot 3- Measurement of iodide uptake 4- Immunofluorescence analysis 5- BCA protein assays kits	Resveratrol	F1 subclone of FRTL-5 rat thyroid cells/ male adult Sprague-Dawley rats	Cesidio Giuliani et al. (2014) [29]
Thyroglobulin, thyroid peroxidase, TSH receptor, Nkx2-1, Foxe1 and Pax8/ No clinical signs of hypothyroidism/ increase in thyroid size/ normal levels of Serum TSH and thyroid hormone/ increased proliferative activity.	1- Real-time quantitative PCR analysis 2- Western blotting 3- TSH and thyroid hormones determination 4- Morphological analysis 5- Chromatographic system (equipped with a fluorescence detector and photodiode array detector) 6- BCA protein assays kits	Resveratrol	Rat thyroid FRTL-5 cell line/ Sprague-Dawley rats	Cesidio Giuliani et al. (2017) [67]
The arrest of cell growth in both papillary and follicular thyroid cancer.	-	Resveratrol	-	LH Duntas (2011) Short Review [29]
Antithyroid effect/ inhibit thyroid hormone. Biosynthesis/ decrease thyroid iodide uptake.	-	Flavonoids	-	Maria Carolina de Souza dos Santos (2011) Review [1]
Soy isoflavones do not adversely affect thyroid function.	Serum Thyroid-Stimulating Hormone (TSH), thyroxine (T4), and triiodothyronine (T3) were measured at baseline and after 90 and 180 days	Isoflavone (SOYFOODS)	Postmenopausal women (64–83 years old)	Bonnie Bruce et al. (2003) [61]
Hypertrophy and/or hyperplasia of the follicles/ Decreased activity of thyroid peroxidase and 50-deiodinase I/ elevated thyroidal Na^+/K^+-ATPase activity/ reduce of serum T3 and T4 levels/significant elevation of serum TSH.	1- Histological study (H&E and PAS) 2- Thyroid peroxidase (TPO) assay 3- Thyroidal sodium, potassium adenosine triphosphatase (Na^+/K^+-ATPase) assay 4- 50-Deiodinase I (50-DI) assay 5- Protein estimation 6- ELISA of serum tri-iodothyronine (T3) and thyroxin (T4) 7- Radioimmunoassay (RIA) of Thyroid Stimulating Hormone (TSH)	Catechins/ green tea	Male albino rats	Amar K. Chandra (2010) [64]
It does not significantly increase the risk of clinical or subclinical hypothyroidism.	1- Serum parameters 2- THRα, THRβ, RARα, RARγ, and RXRα, mRNA Expression	Genistein Aglycone (one type of isoflavones)	Osteopenic, postmenopausal women	Alessandra Bitto (2010) [60]
Chrysin inhibits growth in ATC cells via apoptosis in vitro.	1- Cell Proliferation Assay (MTT) 2- Western Blot Analysis	Chrysin (one type of isoflavones)	HTH7 and KAT18 cells, derived from patients with ATC	Tramanh Phan (2011) [57]
Pigenin and luteolin are the most potent inhibitors of these cell lines.	1- Cell proliferation assays 2- Ligand binding assays	Flavonoids (genistein, apigenin, luteolin, chrysin, kaempferol, and biochanin A)	UCLA NPA-87-1 (NPA) (papillary carcinoma), UCLA RO-82W-1 (WRO) (follicular carcinoma), and UCLA RO-81A-1 (anaplastic carcinoma)	Fen Yin (1999) [58]

on the impact of various plants on the thyroid function are summarized in Table 1.

6. Conclusion

Thyroid gland disorder is among the most prevalent endocrine diseases. Inhibition of the growth of cancer cells of the thyroid by flavonoids is promising; according to prior studies, isoflavones can change the function of endocrine glands, including the thyroid. Herbal remedies often have less toxicity and side effects, compared to other methods. Additionally, they are less invasive and cost-effective. Flavonoids as the most abundant antioxidant compounds in the majority of medicinal plants inhibit cell growth in thyroid tumors.

The natural flavonoids of chrysin can probably be considered as a new medication for the treatment of ATC. Moreover, flavonoids such as apigenin and luteolin are among the strong inhibitors of human thyroid carcinoma cells. In addition to the creation of apoptosis in thyroid cancer cells, experimental data suggested that flavonoids can interfere with the thyroid hormones. Catechin inhibits the activity of thyroperoxidase and reduces T3 and T4 serum levels and increases TSH concentration. Quercetin inhibits iodine uptake and thyroid cell growth, and resveratrol may, among various tumors, inhibit cell growth both in thyroid follicular cancer and papillary thyroid carcinoma with the activation of MAPK signal transduction pathway.

The literature review suggests that herbs have significant impacts on thyroid cancer cells, and it is hoped that, new treatments for various thyroid tumors be discovered by conducting more in-depth research on the impact of various herbs and herbal extracts on thyroid cancer cells.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization: Bahman Jalali Kondori; Methodology: Zoleikha Azari; Writing-review & editing: All authors; Funding Acquisition: Mohammad Hossein Asadi; and Supervision: Bahman Jalali Kondori.

Conflict of interest

The authors declared no conflict of interest.

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