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A REVIEW ARTICLE ON THYROID CANCER

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Abstract:

Thyroid cancer is the most frequent endocrine malignancy, with more than 500,000 cases per year worldwide. Differentiated thyroid cancers are the most common forms with best prognosis, while poorly/undifferentiated ones are rare (2% of all thyroid cancer), aggressive, frequently metastasize and have a worse prognosis. For aggressive, metastatic and advanced thyroid cancer novel antitumor molecules are urgently needed and phytochemical products can be a rational and extensive source, since secondary plant metabolites can guarantee the necessary biochemical variability for therapeutic purposes. Among bioactive molecules that present biological activity on thyroid cancer, resveratrol, curcumin, isoflavones, glucosinolates are the most common and used in experimental models. Most of them have been studied both in vitro and in vivo on this cancer, but rarely in clinical trials. This review summarizes phytochemicals, phytotherapeutics and plant derived compounds used in thyroid cancer.

The molecular abnormalities described here represent a broad effort during the past 20 years to understand the fundamental pathophysiology of thyroid cancer. Whereas early oncogenic events have been identified that probably account for the majority of these tumors, further study is needed to identify the incipient events in the remaining tumors. Just as critical is the need for a more comprehensive understanding of the steps that lead to progression, invasion, metastasis, and occasional dedifferentiation. An integrated framework will be required that merges knowledge of DNA mutations with understanding of the role of epigenetic alterations, changes in miRNA regulation of gene expression, and other fundamental processes that contribute to the malignant phenotype. Clinical trials of therapies to reverse genetic changes and alter complex signaling abnormalities will need to be informed by comprehensive, individualized tumor profiling that will facilitate the selection of the correct combination of therapies for each individual patient, including the identification of patients with sufficiently indolent tumors that no therapy will ever be required.

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INTRODUCTION:

Thyroid cancer is cancer that develops from the tissues of the thyroid gland. Thyroid cancer is a disease in which cells grow abnormally and have the potential to spread to other parts of the body. Risk factors include radiation exposure at a young age, having an enlarged thyroid, family history and obesity. The four main types are papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer. Diagnosis is often based on ultrasound and fine needle aspiration. Screening people without symptoms and at normal risk for the disease is not recommended as of 2017.

Thyroid cancer is a malignancy arising from the thyroid parenchymal cells. Its incidence is steadily increasing worldwide, while the mortality rate has remained stable over the past several years. The clinical Behaviour of thyroid cancer is highly variable, from indolent, slowly progressing tumour to highly aggressive tumour with high mortality rates. There are various new cutting-edge treatment options for advanced thyroid cancer, while there is also evidence against the overtreatment of low-risk thyroid cancers. Hence, a thorough understanding of the types of thyroid cancer and its management is of paramount importance in providing the appropriate treatment to the patient. This activity reviews the incidence, etiology, pathophysiology, diagnosis, and treatment of thyroid cancer and highlights the role of interprofessional communication in optimizing the care of these patients. Globally as of 2015, 3.2 million people have thyroid cancer. In 2012, 298,000 new cases occurred. It most commonly is diagnosed between the ages of 35 and 65. Women are affected more often than men. Those of Asian descent are more commonly affected; with a higher rate of mortality among Filipino females. Rates have increased in the last few decades, which is believed to be due to better detection. In 2015, it resulted in 31,900 death.

Signs and symptoms:

Signs and symptoms are the observed or detectable signs, and experienced symptoms of an illness, injury, or condition.

Signs are objective and externally observable; symptoms are a person's reported subjective experiences. A sign for example may be a higher or lower temperature than normal, raised or lowered blood pressure or an abnormality showing on a medical scan. A symptom is something out of the ordinary that is experienced by an individual such as feeling feverish, a headache or other pains in the body.

ETIOLOGY:

Due to a lack of harmonisation across disciplines, determinant, in its more widely accepted scientific meaning, is often used as a synonym. The main difference lies in the realm of practice: medicine (clinical practice) versus public health. As an example from clinical practice, low ingestion of dietary sources of vitamin C is a known risk factor for developing scurvy. Specific to public health policy, a determinant is a health risk that is general, abstract, related to inequalities, and difficult for an individual to control. For example, poverty is known to be a determinant of an individual's standard of health.

Risk factors may be used to identify high-risk people.

Prognostic Factors for Well-Differentiated Thyroid Cancer

Age appears to be the single most important prognostic factor. The prognosis for differentiated carcinoma (papillary or follicular) without extracapsular extension or vascular invasion is better for patients younger than 40 years. patients with follicular cancer without major capsular invasion or blood vessel invasion. Using these criteria, a retrospective studyof 1,019 patients showed that the 20-year survival rate was 98% for patients with low-risk disease and 50% for patients with high-risk disease.

Some of the common mutations are as follows:

PTC - Point mutation in the BRAF gene leading to BRAF V600E mutant kinase is the most common mutation leading to PTC (29 to 69%) and PTC-associated anaplastic thyroid cancer (0 to 12%). Translocation of the RET-papillary thyroid cancer (RET/PTC) occurs in about 7% of PTC.[6] Mutations in RAS proto-oncogene occur in 10-20% of follicular variant PTC (FVPTC).

FTC - Mutations in RAS proto-oncogene are most common in FTC (40 to 50%). Translocation in PAX8–peroxisome proliferator-activated receptor γ (PPARγ) has been identified in around 30 to 35% of FTC.

Anaplastic - Inactivating mutation of the p53 tumor suppressor gene has been identified in addition to early inactivating mutations in about 50 to 80% of the cases with anaplastic thyroid cancer.Also, 66% of anaplastic thyroid cancers have been identified to harbour mutations in the CTNNB1 gene.[5] RAS mutations are also associated with 20 to 40% of anaplastic thyroid cancers.

MTC - Germline mutations of RET proto-oncogene in inherited forms of MTC (approximately 25% of MTC) and RAS mutations in 25% of MTC.

Risk factors: Female sex, a family history of thyroid cancer, and radiation exposure of the thyroid gland

during childhood are the major risk factors associated with DTC. A recent study showed that thyroid cancer affects both genders equally, as seen in autopsy reports, but it might be detected in women more frequently than men. The difference could be explained by access to medical care.Thyroid cancers are thought to be related to a number of environmental and genetic predisposing factors, but significant uncertainty remains regarding their causes.Environmental exposure to ionising radiation from both natural background sources and artificial sources is suspected to play a significant role, and significantly increased rates of thyroid cancer occur in those exposed to mantle field radiation for lymphoma,and those exposed to iodine -131 following the Chernobyl, Fukushima, and windscale nuclear disasters. Thyroiditis and other thyroid diseases also predispose to thyroid cancer.

EPIDEMIOLOGY:

Thyroid cancer represents 1% to 4% of all malignancies and is the fifth most common cancer in women in the United States. It has a female preponderance of around 3:1. There has been a steady rise in the incidence of thyroid cancer globally; particularly, PTC detection has risenby 240% in the last three decades. This increase in the incidence has been observed in both genders and among all races and is thought to be primarily due to an increasing trend in the rate of diagnostic imaging.PTC is the most common endocrine cancer, responsible for 96% ofall new and 66.8% of deaths due to endocrine cancers. As was mentioned earlier, most thyroid cancers derive from the follicular epithelium, with PTC and FTC being far more common than anaplastic thyroid cancer.

HISTOPATHOLOGY:

PTC: Microscopically, the unique characteristic feature of PTC is papillae formation. A papilla consists of layers of tumour cells surrounding a fibrovascular core. Follicles are typically absent in classic PTC. Typical cellular histomorphology includes cells with large and clear nuclei with finely granular chromatin, often described as ground-glass or "Orphan Annie-eye" nuclei with nuclear grooving and intranuclear inclusion bodies. Psammoma bodies, which are calcified clumps of cells likely derived from necrosed papillae, are also common.Some variants of PTC do not form papillae and are termed follicular variants of PTC, provided they still have the nuclear features of PTC. Variants of PTC such as tall cell variant, columnar variant, insular carcinoma, and diffuse sclerosing variant are more aggressive than classic PTC and are termed thyroid cancers with intermediate differentiation.

FTC: The histological features of FTC can be highly variable, from a well-differentiated follicular pattern to a poorly differentiated pattern with marked nuclear atypia, absence of follicles, extensive capsular or vascular invasion, and solid growth.

Hurthle cell carcinoma: This is characterised by the occurrence of eosinophilic oxyphilic cells with abundant cytoplasm (oncocytes) and prominent nucleoli.

MTC: Given its origin from the parafollicular C cells, its histological features are the presence of spindle-shaped cells with no follicle formation. Amyloid deposition and calcitonin immunoreactivity are typically present.

The most common presenting feature in DTC is either neck swelling (detected by the patient or a clinician) or incidentally detected thyroid nodules on neck imaging. The risk of malignancy of a thyroid nodule in the general population is around 5 to 10%, with the risk being higher in men and extremes of age.

Anaplastic thyroid carcinoma: The usual histologic variants are spindle-cell, pleomorphic giant cell, and squamoid variants. Most of these cancers can consist of a mixed morphologyof 2 or 3 variants. Atypical mitosis and numerous mitotic figures are very common. These cancers are less likely to stain for thyroid transcription factor 1 (TTF1), PAX 8, or thyroglobulin.

DIAGNOSIS:

After a thyroid nodule is found during a physical examination, a referral to an endocrinologist or a thyroidologist may occur. Most commonly, an ultrasound is performed to confirm the presence of a nodule and assess the status of the whole gland. Some ultrasound results may report a TI-RADS or TIRADS score to categorize the risk of malignancy. Measurement of thyroid stimulating hormone, free and/or total triiodothyronine (T3) and thyroxine (T4) levels, and antithyroid antibodies will help decide if a functional thyroid disease such as Hashimoto's thyroiditis is present, a known cause of a benign nodular goiter. A thyroid scan, performed often in conjunction with a radioactive iodine uptake test may be used to determine whether a nodule is "hot" or "cold" which may help to make a decision whether to perform a biopsy of the nodule. Measurement of calcitonin is necessary to excludethe presence of medullary thyroid cancer. Finally, to achieve a definitive diagnosis before deciding on treatment, a fine needle aspiration cytology test may be performed

and reported according to the Bethesda system.

Thyroid cancers can be classified according to their histopathological characteristics. These variants can be distinguished (distribution over various subtypes may show regional variation):

Papillary thyroid cancer (75 to 85% of cases) – is more often diagnosed in young females compared to other types of thyroid cancer and has an excellent prognosis. It may occur in women with familial adenomatous polyposis and in patients with Cowden syndrome. A follicular variant of papillary thyroid cancer also exists.

Newly reclassified variant: noninvasive follicular thyroid neoplasm with papillary-like nuclear features is considered an indolent tumor of limited biologic potential.

Follicular thyroid cancer (10 to 20% of cases) – occasionally seen in people with Cowden syndrome. Some include Hürthle cell carcinoma as a variant and others list it as a separate type.
Medullary thyroid cancer (5 to 8% of cases) – cancer of the parafollicular cells, often part of multiple endocrine neoplasia type 2.

Poorly differentiated thyroid cancerAnaplastic thyroid cancer (1 to 2%) is not responsive to treatment and can cause pressure symptoms.
Others:

- Thyroid lymphoma
- Squamous cell thyroid carcinoma
- Sarcoma of thyroid
- Hürthle cell carcinoma

The follicular and papillary types together can be classified as "differentiated thyroid cancer". These types have a more favourable prognosis than the medullary and undifferentiated types.
Papillary microcarcinoma is a subset of papillary thyroid cancer defined as a nodule measuring less than or equal to 1 cm. 43% of all thyroid cancers and 50% of new cases of papillary thyroid carcinoma are papillary microcarcinoma. Management strategies for incidental papillary microcarcinoma on ultrasound (and confirmed on FNAB) range fromtotal thyroidectomy with radioactive iodine ablation to lobectomy or observation alone.Harach et al. suggest using the term "occult papillary tumor" to avoid giving patients distress over having cancer. Woolner et al. first arbitrarily coined the term "occult papillary carcinoma", in 1960, to describe papillary carcinomas ≤ 1.5 cm in diameter.

Staging

Cancer staging is the process of determining the extent of the development of a cancer. The TNM staging system is usually used to classify stages of cancers, but not of the brain.

Stage groups for papillary or follicular thyroid cancer in a person younger than 55

Stage I: This stage describes a tumor (any T) with or without spread to lymph nodes (any N) and no distant metastasis (M0).
Stage II: This stage describes a tumor (any T) with any metastasis (M1) regardless of whether it has spread to the lymph nodes (any N).

Stage groups for papillary or follicular thyroid cancer in a person 55 and older

Stage I: This stage describes any small tumor (T1) with no spread to lymph nodes (N0) and no metastasis (M0).
Stage II: This stage describes a larger, noninvasive tumor (T2) with no spread to lymph nodes (N0) and no metastasis (M0)
Stage III: This stage describes a tumor larger than 4 cm but still contained in the thyroid (T3) with no spread to lymph nodes (N0) and no metastasis (M0). Or, any localised tumor (T1, T2, or T3) will spread to the central compartment of lymph nodes (N1a) but no distant spread (M0).
Stage IVA: This stage describes a tumor that has spread to nearby structures (T4a), regardless of whether it has spread to the lymph nodes (any N), but it has not spread to distant places (M0). Or, this describes a localised tumor (T1, T2, or T3) with lymph node spread beyond the central compartment (N1b) but no distant spread (M0).
Stage IVB: This stage describes a tumor that has spread beyond nearby structures (T4b), regardless of spread to lymph nodes (any N), but no distant spread (M0).
Stage IVC: This stage describes all tumors (any T, any N) when there is evidence of metastasis (M1).

Stage groups for medullary thyroid cancer

Stage I: This stage describes a small tumor (T1) with no spread to lymph nodes (N0) and no distant metastasis (M0).
Stage II: This stage describes a larger localized tumor (T2 or T3) with no spread to lymph nodes (N0) and no metastasis (M0).
Stage III: This stage describes any localized tumor (T1, T2, or T3) that has spread to the central compartment of lymph nodes (N1a) but has not metastasized (M0).
Stage IVA: This stage describes a tumor that has spread to nearby structures (T4a), regardless of

whether it has spread to the lymph nodes (any N), but it has not spread to distantplaces (M0). Or, this describes a localized tumor (T1, T2, or T3) with lymph node spread beyond the central compartment (N1b) but no distant spread (M0).

Stage IVB: This stage describes a tumor that has spread beyond nearby structures (T4b), regardless of spread to lymph nodes (any N), but no distant spread (M0).

Stage IVC: This stage is used when there is evidence of metastasis (any T, any N, M1).

Stage groups for anaplastic thyroid cancer

Stage IV: All anaplastic thyroid tumors are classified as stage IV, regardless of tumor size, location, or metastasis.

Stage IVA: This stage describes an anaplastic tumor that has spread to nearby structures (T4a), regardless of whether it has spread to the lymph nodes (any N), but it has not spread todistant places (M0).

Stage IVB: This stage describes an anaplastic tumor that has spread beyond nearby structures (T4b), regardless of spread to lymph nodes (any N), but no distant spread (M0).

Stage IVC: This stage is used when there is evidence of metastasis (any T, any N, M1).

Recurrent: Recurrent cancer is cancer that has come back after treatment. If the cancer does return, there will be another round of tests to learn about the extent of the recurrence. These tests and scans are often similar to those done at the time of the original diagnosis.

Metastases

Detection of differentiated thyroid cancer metastases may be detected by performing afull- body scintigraphy using iodine -131

Spread

Thyroid cancer can spread directly, via lymphatics or blood. Direct spread occurs through infiltration of the surrounding tissues. The tumour infiltrates into infrahyoid muscles, trachea, oesophagus, recurrent laryngeal nerve, carotid sheath etc. The tumour then becomes fixed. Anaplastic carcinoma spreads mostly by direct spread, while papillary carcinoma spreads the least. Lymphatic spread is most common in papillary carcinoma. Cervical lymph nodes become palpable in papillary carcinoma even when the primary tumor is impalpable. Deep cervical nodes, pretracheal, prelaryngeal, and paratracheal groups of lymph nodes are often affected. The lymph node affected is usually the same side as that of the location of the tumour. Blood spread is also possible in thyroid cancers, especially in follicular and anaplastic carcinoma. The tumour emboli do angioinvasion of lungs; end of long bones, skull, and vertebrae are affected. Pulsating metastases occur because of their increased vascularity.

TREATMENT:

Papillary and Follicular Thyroid Cancers

● Surgical Treatment

Surgical resection remains the main treatment modality of both PTC and FTC, followed by radioiodine ablation (RAI ablation) when indicated and suppression therapy with thyroid hormone. Systemic radiation and chemotherapy seldom play a significant role in treatment, although they may be used in advanced cases refractory to conventional methods.

To minimise the risk of complications, specifically recurrent laryngeal nerve injury and hypoparathyroidism, surgery is recommended, performed by experienced, "high-volume" thyroid surgeons.

Pre-operative neck ultrasound is pivotal in deciding the appropriate surgical procedure. Surgical resection can be hemithyroidectomy or total thyroidectomy, with or without lymph node dissection. The choice of surgery depends on tumour size, presence of lymph node metastasis, extrathyroidal extension, age of the patient, and the presence or absence ofcomorbid conditions. In patients with locally advanced disease, additional imaging of theneck is advised.

A thyroid lobectomy is preferred for unilateral DTC < 1 cm, without any extra-thyroid or lymph node invasion, unless there are clear indications for total thyroidectomy, such as childhood head and neck irradiation or a strong family history of thyroid cancer. Lately, thereis also a trend for just active surveillance without immediate surgery, but more studies are needed to show the difference, if any, in the outcomes and prognosis.

For tumour sizes between 1 and 4 cm with no extrathyroidal or lymphatic invasion, the procedure of choice can either be a total thyroidectomy or lobectomy, depending on patient preferences and risk factors, as described above. This decision should be made with the patient aware that a complete thyroidectomy may be necessary depending on pathology results.

For tumours > 4 cm or tumours with extra-thyroid or lymph node invasion, a total thyroidectomy is the preferred surgical procedure as there is a high risk of

multifocal carcinoma in such cancers. It is also intended to facilitate RAI ablation and future surveillance with thyroglobulin as a tumour marker.

Postsurgical Risk Stratification

Postsurgical risk stratification must be performed to determine the need for additional treatment, especially with RAI ablation. The TNM (Tumor, Node, Metastasis) risk stratification by the American Joint Commission on Cancer(AJCC) predicts disease-specific mortality, while the American Thyroid Association (ATA) risk stratification system, which is widely used, helps predict the persistence or recurrence of residual cancer.

Radioiodine (RAI) Ablation Therapy

RAI therapy after thyroidectomy is used for remnant ablation of normal residual thyroid tissue, as adjuvant therapy for subclinical micrometastases, or as treatment of apparent local or distant metastasis. High-risk and some selected intermediate-risk patients, per the ATA risk stratification system, will benefit from RAI ablation. Patients who are candidates for RAI therapy should maintain a low iodine diet for 1 to 2 weeks before the treatment to ensure iodine depletion of the cells; they should also be cautioned against large iodineadministrations such as through iodinated contrast or amiodarone to improve the avidity ofthe thyroid follicular cells to iodine.

Thyroid Hormone Suppression Therapy

Thyroid hormone suppression therapy to suppress TSH and thereby potentially minimise its stimulation of thyroid cancer growth is recommended in most patients after surgery. For patients with ATA high-risk, the goal TSH should be no more than 0.1m IU/ litre, and for patients in the intermediate-risk category, the goal TSH should be between 0.1 and 0.5 mIU/litre. For the ATA low-risk category, a goal TSH between 0.5 and 2.0 mIU/litre is acceptable.

Persistent or Recurrent Disease

For recurrent minimal iodine-avid disease, RAI ablation is the preferred therapy. For invasive neck disease, surgical resection is recommended. Percutaneous ethanol injection has been tried for cervical lymph node metastasis. For small distant metastasis to bones or lungs, radiofrequency ablation has been used. Other treatment options are external beam radiation and systemic chemotherapy.

Systemic Chemotherapy

Systemic chemotherapy is usually only considered in a group of carefully selected patients with a high metastatic disease burden or rapidly progressive metastatic disease despite the above treatment (Iodide-refractory). Because of the significant adverse effects associated withsuch therapy, it should be considered only when the associated benefits exceed the risks

Systemic chemotherapy for DTC is preferably administered through a clinical trial. The common agents of choice are the kinase inhibitor class of drugs such as anti-angiogenic multi- targeted kinase inhibitors (aaMKI- lenvatinib, sorafenib), BRAF kinase inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), NTR kinase inhibitors (larotrectinib), and RET inhibitor (selpercatinib).

Dynamic Risk Stratification

After the initial post surgical risk stratification and appropriate treatment as above, patients should be re-stratified during each follow-up visit depending on their response to therapy into one of the following clinical outcomes:

1. Excellent response,
2. Biochemical incomplete response,
3. Structural incomplete response,
4. Indeterminate response.

Medullary Thyroid Cancer

Surgical therapy that includes total thyroidectomy with resection of local and regional metastases is the mainstay of treatment for MTC. In most patients with confirmed MTC and no evidence of pre-operative cervical lymph node metastasis on ultrasound, prophylactic central lymph node dissection should be performed at the time of the total thyroidectomy. Patients with confirmed lateral zone nodal metastases should receive lateral compartment dissection, central neck dissection, and total thyroidectomy. Serum calcitonin, carcinoembryonic antigen, and biochemical testing for coexisting hyperparathyroidism and pheochromocytoma should be performed. Patients should be monitored long-term with serial calcitonin levels, neck ultrasound, and physical examination. .

Anaplastic Thyroid Cancer

In patients diagnosed with anaplastic thyroid cancer, BRAF V600E mutation testing and staging are performed. Resectable disease is surgically removed, followed by specific BRAF kinase inhibitors in patients with BRAF V600E mutations. Other patients received targeted radiation treatment

and cytotoxic chemotherapy after surgery.

Targeted Drug Therapy for Thyroid Cancer
The types of targeted drugs used to treat thyroid cancer are known as kinase inhibitors. Kinases are proteins inside cells that normally relay signals (such as telling the cell to grow). Blocking certain kinases can help treat some cancers.

Multikinase inhibitors
Lenvatinib (Lenvima), sorafenib (Nexavar), and cabozantinib (Cabometyx) are targeted drugs known as multikinase inhibitors, because they can block several different kinase proteins. These drugs work in 2 main ways:
Lenvatinib and sorafenib can often help stop cancer growth for a time in people with differentiated thyroid cancer (papillary or follicular thyroid cancer) whose treatment with radioactive iodine is no longer working. If these drugs are no longer helpful, cabozantinib may be an option.

TRK inhibitors
A small number of thyroid cancers have changes in one of the NTRK genes. These gene changes can help cancer cells grow.

Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) target and disable the abnormal TRK proteins made by the NTRK genes. These drugs can each be used in people with advanced thyroid cancer that has an NTRK gene change and is still growing despite other treatments..
Multikinase inhibitors

Vandetanib (Caprelsa) and cabozantinib (Cometriq) are multikinase inhibitors (drugs that target several different kinase proteins). They can affect both cancer cells themselves and the growth of new blood vessels (which tumors need to grow).These drugs can be used to treat advanced MTC. They each can stop cancers from growing for a time, although it is not yet clear if they can help people live longer.

RET inhibitors
In some medullary thyroid cancers, the cells have certain changes in the RET gene that cause them to make an abnormal from of the RET kinase protein. This abnormal protein helps the cells grow. Selpercatinib (Retevmo) is a type of drug known as a RET inhibitor. It works by attacking the RET protein. This drug can be used to treat advanced MTC if the cancer cells have certain types of RET gene changes.

BRAF and MEK inhibitors
Some anaplastic thyroid cancers have changes in the BRAF gene, which causes them to make certain proteins that can help them grow. Dabrafenib (Tafinlar) and trametinib (Mekinist) are drugs that target some of these proteins. (Dabrafenib affects the BRAF protein, while trametinib targets the related MEK protein.) These drugs can be used together to treatanaplastic thyroid cancers that have a certain type of BRAF gene change and that can't be removed completely with surgery.

Drugs Approved for Thyroid Cancer
This page lists cancer drugs approved by the Food and Drug Administration (FDA) for thyroid cancer. The list includes generic names and brand names. The drug names link to NCI's Cancer Drug Information summaries. There may be drugs used in thyroid cancer that are not listed here.

Drugs Approved for Thyroid Cancer:

- Cabozantinib-S-Malate
- Caprelsa (Vandetanib)
- Cometriq (Cabozantinib-S-Malate)
- Dabrafenib Mesylate
- Doxorubicin Hydrochloride
- Gavreto (Pralsetinib)
- Lenvatinib Mesylate
- Lenvima (Lenvatinib Mesylate)
- Mekinist (Trametinib Dimethyl Sulfoxide)
- Nexavar (Sorafenib Tosylate)
- Pralsetinib
- Retevmo (Selpercatinib)
- Selpercatinib
- Sorafenib Tosylate
- Tafinlar (Dabrafenib Mesylate)
- Trametinib Dimethyl Sulfoxide
- VandetanibHERBAL DRUGS:

Table : Phytochemicals for the treatment of thyroid cancer

Phytochemicals	Cell lines/patient	Dose (μM)	Mechanisms
EGCG	TPC-1, ARO	10~200	Induce apoptosis via inhibiting EGFR/RAS/ERK pathway
Resveratrol	TPC-1, BCPAP	5~50	Induce apoptosis and differentiation of CSC
Punicalagin	BCPAP	12.5~100	Induce cell death by triggering ATM-mediated DNA damage; inhibit senescent growth via NF-*κ*B pathway.
Curcumin	TPC-1, BCPAP, K1	12.5–50	(1) induction of ROS-independent DNA damage by triggering an ATM-activated Chk2-Cdc25C-Cdc2 pathway; (2) activation of ER stress by disruption of intracellular calcium homeostasis; (3) inhibition of *β*-catenin pathway; (4) modulation of mitochondrial Bcl-2/Bax pathway.
Apigenin	BCPAP	12.5~100	Arrest the cell growth in G2/M phase; induce autophagy via ROS-mediated DNA damage.
Quercetin	BCPAP	50-75	Induce apoptosis via inhibiting Hsp90 and caspase-3/parp pathways
Genistein	BHP10-3, BCPAP, IHH4	9.5–300	Inhibit β-catenin and EMT

Traditional herbal medicine has an important position in PTC prevention and treatment in Asian countries for a long history. Many active ingredients derived from food and herbs could prevent the development of PTC. Characterised by their mildness and long-lasting action, limited side effects, long-term use, and multitarget regulation, these herbal active ingredients provide many advantages and cannot be replaced by western medicine.

Tannins (phenolic acids)

On the basis of their chemical structure, tannins can be categorised into hydrolyzable, condensed, and complex tannins. Condensed tannins manifest numerous pharmacological effects, such as antioxidant, antitumor, anti human immunodeficiency virus, anti- inflammatory, and antimicrobial properties, and are widely found in many medicinal plants and dietary sources, including fruits, nuts, grains, spices, and beverages. Epigallocatechin-3- gallate (EGCG), which is the major catechin in tea, shows remarkable protective effects against several chronic inflammatory and cardiovascular diseases, such as cancer, obesity, diabetes, myocardial ischemia, bronchitis, and asthma . EGCG exerts chemopreventive effects on various tumors and selectively inhibits various cancer cell proliferation, metastasis, and invasion via regulating VEGF, MAPK, PI3K, and Wnt pathways. Wu et al. treated human PTC cell lines (TT and TPC-1) and the ATC cell line (ARO) with EGCG at concentrations of 10~200 μM and observed that EGCG concentration-dependently inhibited the proliferation of these PTC cells and made the cell cycle arrest at the S phase. Resveratrol is a polyphenolic phytoalexin with antioxidant and chemopreventive activities . This material has a wide spectrum of targets, including COX2, Sirt1, p53, and

miR-17/miR-20b , and can inhibit multiple cellular signaling pathways, which were associated with carcinogenesis and progression .

Punicalagin is a large polyphenol compound extracted from pomegranates and is classified as an ellagitannin, a family of hydrolyzable tannins. Punicalagin not only induces the cell death of the PTC cell line BCPAP by triggering ATM-mediated DNA damage response but also leads to the G0/G1 phase arrest and senescence-associated secretory phenotype by triggering NF-κB activation.

Flavonoids

Flavonoids are a group of phenolic antioxidants with strong biological activity that have been widely used in pharmaceutical and food additives.

Some flavonoids, such as soy genistein, naringenin, phloretin, and chrysin, are structurally similar to oestrogen and have little or weak oestrogen-like effects .

Apigenin and quercetin are flavonoids that are most commonly found in a variety of fruits, vegetables, and herbs .

Icariin is the main active ingredient of Epimedium davidii Franch. and has gained much attention because of its erectogenic and neurotrophic effects . Recently, many studies have demonstrated the application of icariin on hormone-dependent neoplasia and in the treatment of prostatic, ovarian, and thyroid cancers . Icariin can inhibit cell proliferation, migration, and invasion via downregulating miR-625-3p and suppressing PI3K/AKT and ERK pathways in both SW579 and TPC1 cells.

Flavokawain B is a hepatotoxic constituent extracted from kava root and shows potent cytotoxicity by inducing ROS-mediated apoptotic and autophagic cell death in various tumor cells.This material also inhibits cell viability, migration, and invasion and causes autophagy via the activation of the AMPK/mTOR pathway in thyroid cancer ARO, WRO, and TPC-1 cells .

Genistein is the main active ingredient of Leguminosae. This isoflavone inhibits the invasion and metastasis of the PTC-derived BHP10-3 cell (with RET/PTC 1 rearrangement), BCPAP, and IHH4 (with BRAFV600E mutation) by inhibiting β-catenin and EMT [46]. However, genistein upregulates most thyroid transcript signals, except for thyroid peroxidase, in zebrafish embryos, thereby indicating potential disruptions

Silibinin is a natural hepatoprotective drug and has excellent antioxidant and anticancer properties. It also induces apoptosis, autophagy, makes cell cycle arrest, and inhibits onco- miRNAs which are involved in the PTC tumorigenesis .

Previous studies showed that it suppressed cell migration and MMP-9 expression by regulating the ERK pathway in thyroid cancer cells.

Saponins

Saponins are steroid or triterpenoid glycosides commonly found in plants. Extensive studies have shown that saponins have various pharmacological effects, including hypoglycemic, antitumor, anti-inflammatory, immunomodulatory, and vasoprotective properties, and thus they have been widely used for preventing and treating cardiovascular and immunodeficiency diseases . Ginsenosides are by far the most investigated group of saponins with a triterpenoid dammarane skeleton and are the main active ingredients of the ginseng genus (Panax ginseng

C. A. Mey. Panax notoginseng (Burk.) F. H. Chen and Panax quinquefolium L.) in Araliaceae and Gynostemma pentaphyllum (Thunb) Makino. in Cucurbitaceae .

MEDICINAL HERBS:

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 . There are more than 20000 species of plants used as traditional medicine. Over 3000 plants with anticancer properties are identified throughout the world . Based on studies, more than 30% of cancer patients use herbal extracts for treatment.

Herbal plants 1.Camptotheca acuminata:

20-(S)-Camptothecin (CPT) is a natural alkaloid extracted from the bark of Camptotheca acuminata (Chinese happy tree). It acts as a DNA topoisomerase 1 poison with an interesting antitumor activity and its use is limited by low stability and solubility and unpredictable drug- drug interactions. Since the late 20th century, it has been widely used in cancer therapy and, since extraction yields from plant tissues are very low, various synthetic routes have been developed to satisfy the increase in demand for CPT. Moreover, SAR studies have allowed for the development of more potent CPT analogues topotecan and irinotecan. Unfortunately, resistance has already occurred in several tumour lines. Irinotecan (CPT-11) isa semisynthetic derivative of camptothecin, an alkaloid

extracted from the Chinese plant Camptotheca acuminata.

2. Pomegranate

The name pomegranate derives from mediaeval Latin pōmum "apple" and grānātum "seeded".[7] Possibly stemming from the old French word for the fruit, pomme-grenade, the pomegranate was known in early English as "apple of Grenada"—a term which today survives only in heraldic blazons. This is a folk etymology, confusing the Latin granatus with the name of the Spanish city of Granada, which is derived from an unrelated Arabic word.Pomegranate peel has substantial amounts of phenolic compounds, such as hydrolysable tannins (punicalin, punicalagin, ellagic acid, and gallic acid), flavonoids (anthocyanins and catechins), and nutrients, which are responsible for its biological activity.

Punicalagin (PUN), a component derived from pomegranate, is well known for its anticancer activity. Our previous work revealed that PUN induces autophagic cell death in papillary thyroid carcinoma cells.

3. Allium cepa

Kaempferol, ferulic acid, quercetin, gallic acid, and protocatechuic acid were also identified. The number of phenolic compounds found in each variety varied significantly, e.g., gallic acid (9.3–354 lg/g), ferulic acid (13.5–116 lg/g), quercetin (14.5–5110 lg/g), protocatechuic acid (3.1–138 lg/g), and kaempferol (3.2–481 lg/g)

Cancer can be described as the uncontrolled proliferation of abnormal cells in almost every organ or tissue of the body. According to WHO, cancer was the second leading cause of death in 2018, and globally around 10 million people died from cancer in 202056. The present anticancer drugs have low pharmaceutical indexes which means that, at higher doses, they can cause adverse side effects such as cardiomyopathy, neuropathy, bone marrow depression, kidney damage, liver damage, and anaemia . Again, resistance to anticancer medications has often been a challenge in the modern therapeutic period , which is why several studies have been performed in recent years to promote the use of natural products such as herbs andplants as cancer therapy substitutes, as well as their use as dietary supplements to minimise the progression of cancer]. Studies suggest that *A. cepa* (onions) have anticancer and similar biological properties, which are thought to be attributed to the presence of different organosulfur derivatives, flavonoids, polyphenols, quercetin, and its glycosides . onions are powerful anticarcinogens which are due to their function in the activation of detoxifying enzymes that significantly eliminate cancer-causing substances .

4. Barberry

Berberine (BBR) is a phytogenous alkaloid that can be isolated from many vegetable species including barberry (Berberis), meadow rue (Thalictrum), celandine (Chelidonium), goldenseal (Hydrastis canadensis L.), and Phellodendron amurense. Berberine Inhibited the Growth of Thyroid Cancer Cell Lines 8505C and TPC1.Berberine, isolated from the roots of herbal plants, is a natural compound that is non-toxic to humans. Berberine has been used as an agent for the treatment of inflammatory disease such as rheumatoid arthritis due to its anti- inflammatory activities. Berberine also can control several physical activities, including lowering-cholesterol and maintenance of insulin levels. Anti-cancer activity of berberine against a variety of cancer cell lines has been introduced.

5. Curcuma longa

Curcumin [diferuloylmethane: (1E, 6E) -1,7-bis (4-hydroxy-methoxyphenyl) -1,6-heptadiene-3, 5-dione] is the active ingredient of the dietary spice found in the rhizomes of Curcuma longa (Curcuma longa L.), a plant in the ginger family. Turmeric, a common oriental spice that gives curry powder its yellowish color, is frequently used in Asian cooking, particularly Indian, Pakistani, and Thai cooking. The active ingredients are made up mainly by curcuminoids, desmethoxycurcumin, bisdemethoxycurcumin and curcumin. Curcumin is a lipophilic phenolic substance that has attracted great attention from the scientific community for its many beneficial biological properties. For its intense yellow color curcuma is used for dying purposes, especially in the food industry. Numerous studies have indicated that curcumin possesses a wide variety of biological functions, such as anti-inflammatory, anti- cancer, anti-oxidant, antimicrobial, wound-healing and hypoglycemic activities .

6. Soybean

Amounts of genistein and genistin in soybeans, soy nuts and soy powder were in the range of
4.6 to 18.2 and 200.6 to 968.1 μg/g of food, respectively. The values for soy milk and tofu (bean curd) were 1.9 to 13.9 and 94.8 to 137.7 μg/g food, respectively. is the most extensively studied

Genistein (4',5,7-trihydroxyisoflavone) soy isoflavone, which is mainly absorbed from the intestine and is readily bioavailable. This makes it a promising candidate for disease prevention

Owing to its structural similarity to endogenous estrogen 17 estradiol, Genistein is also called phytoestrogens and could bind with estrogen receptors and activate its downstream signaling pathway . Lu *et al.* found when the mice were administered with genistein at 100 mg/kg, the serum concentrations of genistein was at an average of approximately 60 ng/ml, and stachyose could enhance the absorption of genistein in mice . Genistein was shown to be a potent inhibitor of the tyrosine-specific protein kinase *RET*, and has been used for clinical treatment of prostate carcinoma and non-small cell lung cancer .

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