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Review

Plant natural products with anti-thyroid cancer activity

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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 purpose. Among bioactive molecules that present biological activity on thyroid cancer, resveratrol, curcumin, isoflavones, glucosinolates are the most common and used in experimental model. Most of them have been studied both *in vitro* and *in vivo* on this cancer, but rarely in clinical trial. This review summarizes phytochemicals, phytotherapeutics and plant derived compounds used in thyroid cancer.

1. Introduction

Thyroid cancer is the most frequent endocrine malignancy in humans and accounts for 1% of all cancers in the world. The incidence of thyroid cancer has increased dramatically in the last fifty years [1,2]. Thyroid cancer is the 5th most common cancer in women, accounting for 5% of all new cancers diagnosed in 2012 [1,2]. Primary malignant thyroid cancer can be subdivided in epithelial derived forms, such as papillary thyroid cancer (PTC), Hürthle cell cancer (HCC), follicular thyroid cancer (FTC), anaplastic thyroid cancer (ATC), in parafollicular derived forms, such as medullary thyroid cancer (MTC), or in non-epithelial forms, such as lymphoma, sarcoma and teratoma. Among epithelial, PTC, FTC, HCC are well-differentiated tumors (differentiated thyroid cancer, DTC), while ATC is a highly malignant neoplasm. PTC is the most common malignant tumor of the thyroid gland [3] with 80% of occurrence, followed by FTC, up to 11%, Hürthle cell cancer (HCC, 3%) and ATC (2%) [2]. The standard approach to thyroid cancer treatment as well as novel therapies has been intensively reviewed and analyzed in previous works [1,2]. Although most patients with thyroid cancers exhibit a good prognosis with standard treatment, there are few therapies of proven efficiency for patients with ATC or with advanced, metastatic or recurrent thyroid cancer [4]. With progression in the knowledge of the molecular pathogenesis of thyroid cancer, novel targeted therapies have been developed for advanced and metastatic

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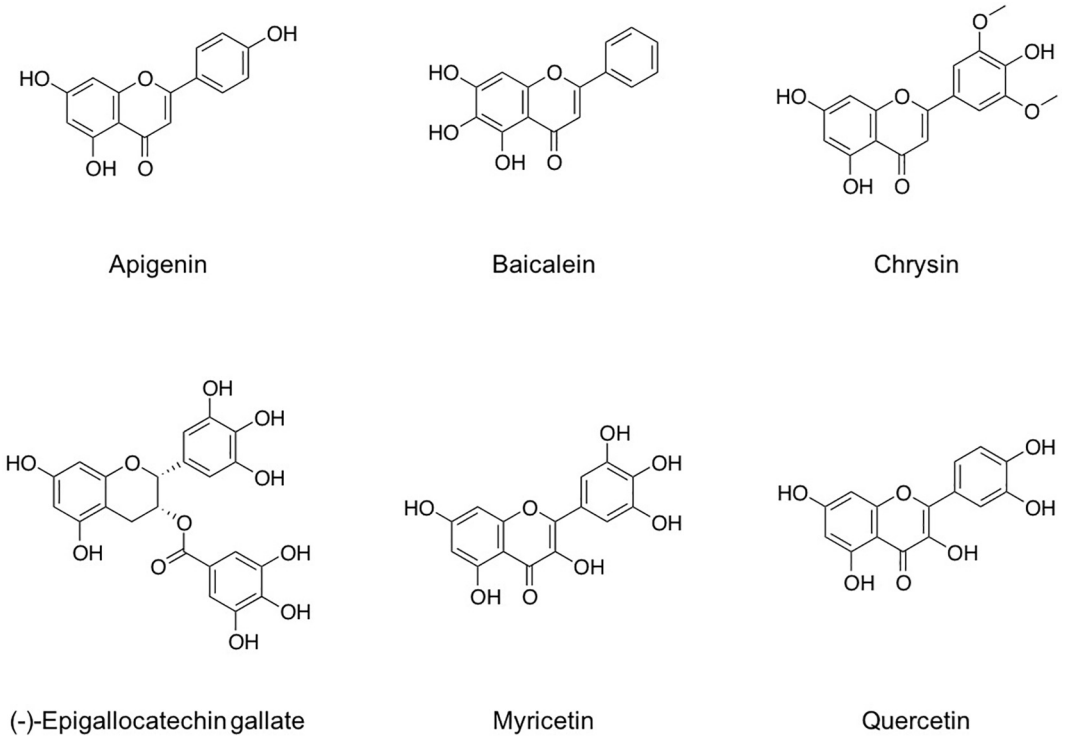

Fig. 1. Schematic representation of main phytochemicals used in thyroid cancer.

thyroid cancer [5]. Some of these drugs have successfully prolonged progression-free survival and have been now Food and Drug Administration approved. Some of them have been tested as multikinase inhibitors, such as vandetanib, cabozantinib, and sorafenib. [6]. Also, other additional agents are being currently under investigation [5].

Current treatment approach for DTC includes surgery, thyroid-stimulating hormone (TSH) suppression, radioactive iodine, external beam radiotherapy, or systemic treatments such as kinases inhibitors. Radioactive iodine therapy (RAI) is the primary first-line systemic treatment for advanced DTC. Nonetheless, during the course of the treatment, the tumor may become refractory to RAI, especially in elderly patients, which are more prone to develop a refractory disease [3]. The advent of TKIs (tyrosine kinase inhibitors) and their usage in RAI refractory disease has improved the progression-free survival [7]. These agents are, however, associated with increased toxicity. The variable nature of disease and toxicity associated with the systemic therapy makes it important to have an individualized approach to the management and treatment of advanced thyroid cancer, especially in the elderly population who can be more susceptible to toxicity [3]. Thus the development of novel therapeutic approaches is needed and plants represent a wide source of scaffolds to dig in to find new drugs. Currently, more than 60% of anticancer compounds that can be considered useful for cancer patients derive from herbal, marine and microorganism sources [8]. The therapeutic efficacy of plants in cancer have been studied extensively and has shown interesting results [9]. It should be noted that some currently used anticancer agents have been developed from plants such as vinblastine, vincristine, taxol and camptothecin [8,10]. Furthermore numerous phytochemicals with potential anti-cancer effects have been studied in most frequent tumors (*i.e.* lung, colon, breast, prostate, *etc.*) and only in turn tested in thyroid cancer. However during the past decade, the increase of works dedicated to thyroid cancer introduced some interesting exceptions, that are extensively discussed below. For example, quercetin induced the differentiation of NIS (sodium iodine symporter) in PTC cells, apigenin increased iodine influx rate in PTC cells, myricetin enhanced iodine retention and increased the influx and decreased the efflux *via* Na^+/I^- symporter in FTC cells. These examples suggest that there is the possibility to target directly thyroid cancer. Nonetheless plant natural compounds used in most widespread tumors frequently impact on the same target or signaling pathway shared with thyroid cancer (MAPK, AKT/mTOR, apoptosis key factors, *etc.*). In the near future it will be necessary to develop novel plant derived molecules with specific thyroid organotropism, focused with high specificity to this subtype of cancer. Unquestionably this raises issues for the develop of anti-cancer agents derived from plants, since a molecule that acts on unhealthy thyroid gland will also affect thyroid hormones (release, storage, synthesis and effects) and iodine metabolism. Such alterations can lead to hyper or hypothyroidism and thus add to the cancer itself with all-encompassing consequences. In addition, it should be considered that, as above reported, there are different thyroid cancer types with different molecular and genetic background to be kept in mind whenever wanted to test a new plant derived compound. Future preclinical and clinical experimentation will have to face with these intriguing challenges and only a research so committed will be successful.

The objective of this review is to summarize phytochemicals used against epithelial and parafollicular derived forms of thyroid cancer, searching for different databases, namely Embase, Google Scholar, Ovid, Pubmed, Scifinder, Science Direct, Scopus, Web of Science. Only articles in English language have been selected, excluding patents and symposium or congress papers. This review focuses on phytotherapeutic agents (plant kingdom) with a possible role in human health, and excludes different compounds derived from other kingdoms of nature. Moreover, it does not investigate the use of phytotherapeutic agents in animals, plants or other organisms which may potentially benefit from herbal products.

2. Phytotherapeutic agents against thyroid cancer subtypes

Phytotherapeutic agents, or herbal remedies, herbal products, herbal medicinal products, phytomedicines, phytopharmaceuticals, are a wide group of plant-derived compounds with potential therapeutic effects in other organisms. These agents play a key role in

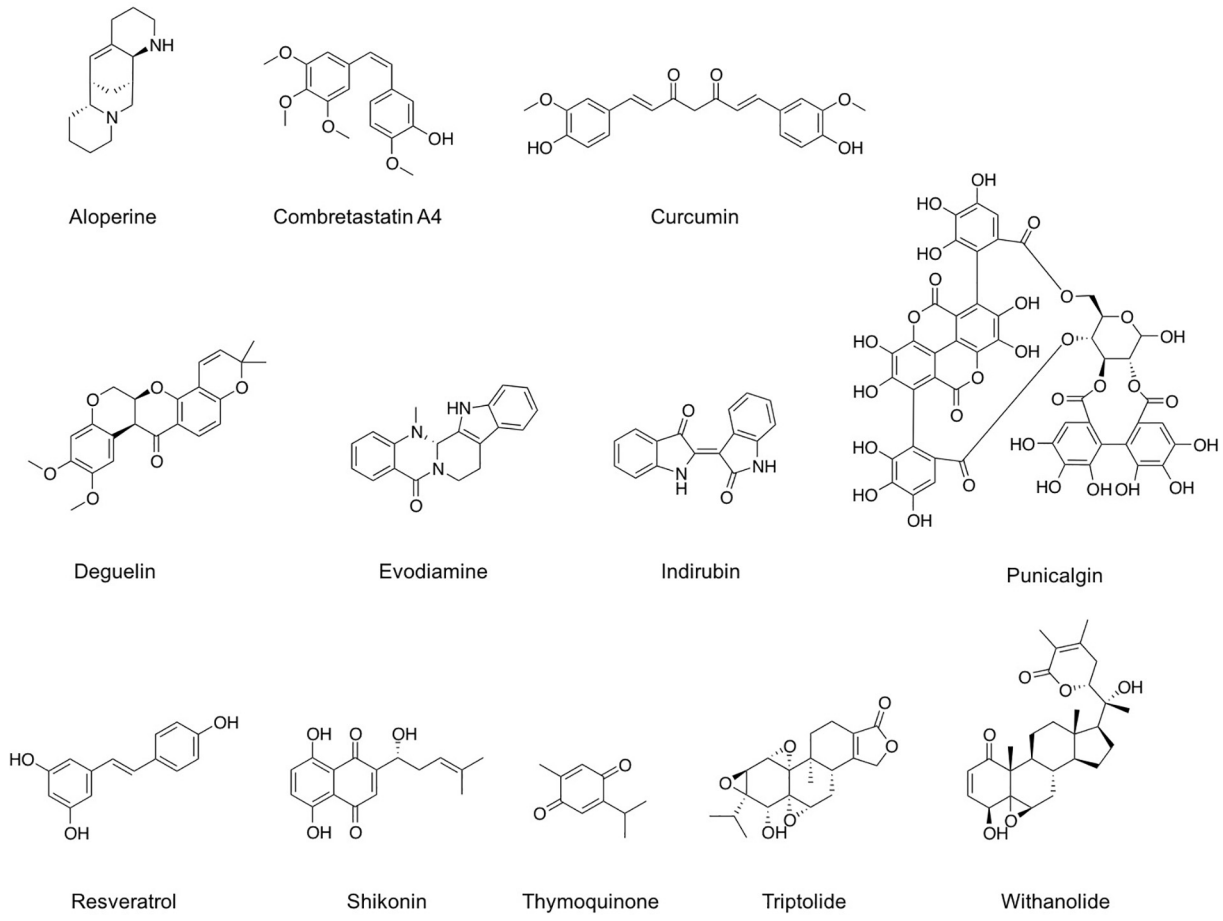

Fig. 2. Schematic representation of main phytochemicals used in thyroid cancer.

phytotherapy, the use of plant material or plant extracts in therapeutic doses to treat symptoms or diseases. This paragraph summarized rational and evidence-based research on the use of phytotherapeutic agents in preclinical models of thyroid cancer subtypes (Fig.1 and 2). (See Fig. 2.)

2.1. Papillary thyroid cancer models

PTC is the most common histologic subtype of thyroid cancer, accounting for 90% of new cases, and shows the best prognosis [11]. PTC subtypes encompass the classic type and follicular variant, whereas tall cell variant (TCV) comprises approximately 6% to 8% of PTC. Other variants are present, but they are less common and represent < 5% [12,13]. TCV, the most common aggressive variant of PTC, frequently has vascular invasion, extrathyroidal extension, lymph node metastasis, and distant metastases [14]. The etiology of PTC is related to environmental, genetic and hormonal factors [15,16]. PTC patients usually present a palpable nodule in the thyroid. Non-palpable nodules may be discovered incidentally after computerized tomography (CT) and magnetic resonance imaging (MRI) examination. Small nodules of PTC or microcarcinomas (less than 1 cm in size) are usually of no clinical significance especially in young patients (less than 40 years) [17]. A few patients may present with cervical lymphadenopathy. Involvement of the Delphian lymph node is an adverse prognostic sign in PTC and may suggest advanced disease with a need to examine the central and lateral lymph node compartments more carefully [18]. For convenience and rapid consultation, a table summarized the phytochemicals used in PTC models (Table 1).

2.1.1. Resveratrol

Resveratrol is a phytoalexin that occurs naturally in grapes and several medicinal plants [19,20]. Resveratrol has a wide variety of biological effects including antioxidant, anti-inflammatory, anticancer, cardio-protector, neuro-protector and anti-diabetic activities [21]. It is also considered as a strong inhibitor of initiation, promotion, and progression of tumors, while the exact molecular mechanism of action is still under investigation [22]. Resveratrol induces apoptosis and cell cycle arrest [23] and has antiproliferation and redifferentiation effects in thyroid cancer cell lines [24]. PTC cells (BHP 2–7 and BHP 18–21) treated with resveratrol (1 to 10 μM) showed a MAPK (mitogen activated protein kinase) activation with a subsequent increase of nuclear p53 protein through Ras-MAPK kinase-MAPK signal transduction and increase of proapoptotic agents (c-fos, c-jun, and p21) [25]. The same authors reported that p53 was a substrate for activated MAPK [26]. In PTC-1 cells treated with 10 μM resveratrol, the phytoalexin stimulated cell growth, whereas higher cocnentration (50 μM) showed inhibitory effects [24]. This hormetic effect should to be carefully considered in future experimentation, in particular when pharmacokinetic studies will need to define a right concentration in human blood to avoid unwanted side effects.

2.1.2. Curcumin

Curcumin is a polyphenol derived from the rhizomes of *Curcuma longa* L. (turmeric) with potent antioxidative and anti-inflammatory properties and involved in anti-diabetic and anticancer activities [27]. Curcumin has been shown to inhibit reactive oxygen species (ROS) up-regulation and reduced the binding capacity of hypoxia-inducible factor-1α (HIF-1α) to hypoxia response element (HRE) in K1 PTC cells in hypoxia conditions [28]. Furthermore, curcumin enhanced E-

Table 1
Anti-cancer effect of phytochemicals in papillary thyroid cells (PTC).

Phytochemicals	Experimental model	Anti-cancer effects	References
Resveratrol	BHP 2–7 and BHP 18–21 cells	• MAPK activation • Increase of nuclear p53 protein • Increase of proapoptotic agents (c-fos, c-jun, and p21) • Apoptosis induction	[19,20]
	TPC-1 cells	• Effective for of TPC redifferentiation therapy • Inhibitory effects in TPC-1	[21]
Curcumin	K1 cells	• Hypoxia-induced migration • Hypoxia-induced ROS upregulation • Reduced HIF-1α binding capacity • Enhanced E-cadherin expression • Inhibited metalloproteinase-9 (MMP-9 activity) • Potential anti-metastatic agent	[22]
	K1 cells	• Inhibited metastasis *via* up-regulation of E-cadherin • Inhibited the expression of MMP-9	[23]
	K1 cells	• Cell viability inhibition • Apoptosis induction in a dose-dependent manner • Induced intracellular formation of ROS • Collapse of MMP • Induced the disturbance of intracellular Ca^{2+} concentration • Bcl-2 and PARP expression modulation	[24]
	BCPAP cells	• Metastasis mechanism *via* TGF-β1/smad2/3 signaling pathway • Adhesion, spreading and migration inhibition • Cell cycle arrest in G2/M phase • Apoptosis induction	[25,26]
	TPC-1 cells	• Cell cycle arrest in G2/M phase • Apoptosis induction • Induced the expression of NF-κB • Cyclin D1 down-regulation	[27,28]
	TPC-1 cells	• Cell survival reduction • Bcl2, cyclin D1, β-catenin, p21 and p53 levels decrement	[29]
Quercetin	BCPAP cells	• Cell proliferation inhibition • Apoptosis induction by down-regulation of the expression of Hsp90 • Cell cycle arrest in S phase • Decreases proteasome activity	[30,31]
	TT cells	• Enhance hyperthermia by down-regulating Hsp70	[32]
	NPA cells	• Induced the differentiation of NIS (sodium iodine symporter) marker • Decreased the expression of CD97	[21]
	K1 and BCPAP cells	• Cell proliferation rate decrement • Increase of E-cadherin expression • Decrease of N-cadherin expression	[33]
Apigenin	PCCl3 rat thyroid cells	• Increased the iodide influx rate • Inhibited the Akt	[34]
	BCPAP cells	• Cell cycle arrest in G2/M phase • Down-regulation of Cdc25C expression	[35]
Punicalagin	BCPAP cells	• Cell viability reduction • Autophagic cell death • Cell cycle arrest in G0/G1 phase • Induced the senescent *via* NF-κB	[36,37]
	BCPAP	• Promoted cell death *via* triggering ATM-mediated DDR • Mitochondrial membrane potential (ΔΨm) decrement and apoptosis induction • migration and invasion reduction by down-regulation of MMP-9	[38] [39]
Isoflavones (cD-tboc)	Primary cultures	• Cell growth inhibition • Estrogen receptor β inhibition • Apoptosis induction	[40]
	Primary cultures	• Cell proliferation inhibition	[41]
	Primary cultures	• Cell proliferation inhibition • No genotoxic damage in DNA	[42]
	BCPAP and IHH4 cells	• Cytoplasmic translocation of β-catenin • Downregulation of cyclin B1 and cyclin A2 • Cell cycle arrest in G2/M phase	[43]
Glucosinolates	B-CPAP and 8505-C cells	• Anti-proliferative effect of 3,3′-diindolylmethane (DIM)	[44]

cadherin expression, inhibited metalloproteinase-9 (MMP-9) activity and suppressed the K1 cells migration ability, suggesting a potential anti-metastatic effect. In a similar study performed in K1 cells, curcumin (12.5, 25 and 50 μM) hampered metastasis *via* up-regulation of E-cadherin expression levels and down-regulation of the activity and expression of MMP-9 [29]. Similarly in K1 cells, the effects of curcumin (10–50 μM) on apoptosis and its potential mechanisms were investigated [30]. In this study, curcumin prompted intracellular formation of ROS and induced apoptotic process, with a subsequent collapse of MMP and intracellular Ca^{2+} influx. Moreover, it was observed that curcumin could affect the expression of apoptosis-related proteins Bcl-2 and poly ADP-ribose polymerase (PARP). In other PTC cell line (BCPAP), curcumin (12.5, 25 and 50 μM) showed anti-metastatic potential *via* transforming growth factor beta 1 (TGF-β1)/smad2/3 signaling pathway [31]. The results revealed that curcumin inhibited the adhesion, spreading and migration of BCPAP cells *via* inhibition of the TGF-β1-induced epithelial-mesenchymal transition through down-regulation of Smad2/3 signaling pathways. Moreover, curcumin (12.5 to 50 μM) activated cell apoptosis cascade through G2/M phase cell cycle arrest [32]. In addition, other important cell factors have been

implicated in curcumin effects. For example nuclear factor-κB (NF-κB) has an important role in cancer cells, indeed its activation is associated with aggressive tumor growth [33]. In PTC cell line (PTC-1) curcumin 50 μM increased the expression of redifferentiation markers and induces G2/M arrest, apoptosis, and down-regulated NF-κB expression [34]. Furthermore, curcumin 25 μM revealed anti-inflammatory and antioxidant properties, while inhibiting cell cycle progression by down-regulating cyclin D1 in TPC1 cell line [35]. Radiosensitive effect of curcumin (5, 10 and 25 μg/mL) on human thyroid cancer cells (Thr.C1-PI 33) treated with ^{131}I was explored showing that curcumin significantly reduced Thr.C1-PI 33 growth in combination with ^{131}I [36]. Another work showed that the polyphenol at 25 μM led to a reduction in the survival of PTC1 tumor cells through a significant reduction of Bcl2 and cyclin D1 levels, as well as of p21 and p53 levels. Another cell multifunctional protein strongly reduced was β-catenin, a molecule involved in cell growth, embryonic development and tissue homeostasis [37].

2.1.3. Quercetin

Quercetin is a natural flavonoid found in the human diet. As a glycoside can be recovered within a variety of plants, fruits and vegetables (*i.e.* onion, buckwheat and broccoli) [38]. Quercetin is known as an inhibitor of heat shock protein (Hsp) and has been tested also in cancer therapy [39]. In preclinical model of PTC, quercetin inhibited BCPAP cell proliferation and triggered apoptosis at 50 and 75 μM concentrations, but only at 75 μM cells were arrested in the S phase [40]. Moreover, it was observed that quercetin induced apoptosis by down-regulation of Hsp90 expression and decreased chymotrypsin-like proteasome activity. In another study on BCPAP cells, quercetin (10 to 75 μM) showed very similar outcomes, underlining the consistency of results [41]. In TT cell line, quercetin was used to enhance hyperthermia, a new strategy for thyroid cancer treatment, by down-regulating Hsp70 [42]. Moreover in NPA cells, quercetin increased or induced the differentiation marker NIS (sodium iodine symporter) and decreased the expression of the de-differentiation marker CD97 [24]. In K1 and BCPAP cells treated with sorafenib 0.1 μM and quercetin 25 μM for 24 h, a decrease in cell proliferation rate was observed, with a significant increase of E-cadherin and concomitant decrease of N-cadherin expression, indicating a reduced epithelial-mesenchymal transition [43]. These data showed that quercetin could lead to similar results in different cell models and this suggests a common mechanism of action shared by the models.

2.1.4. Apigenin

Apigenin is natural flavonoid polyphenol [44]. Numerous studies have confirmed that the flavone apigenin possessed antioxidant, antimutagenic, anticancer, anti-inflammatory, anti-proliferative and anti-neoplastic progression properties [45,46]. In PCCl3 rat thyroid cells, apigenin enhanced the iodide influx rate, increased by AKT inhibition under acute thyrotropin stimulation [47]. Moreover, in BCPAP cell line apigenin provoked a significant accumulation of cells in the G2/M phase by down-regulation of Cdc25C expression [48]. Furthermore, apigenin inhibited PTC cell viability by ROS production stimulation, induced DNA damage and led to autophagic cell death [48].

2.1.5. Punicalagin

Punicalagin is an ellagic acid and gallic acid derived compound from *Punica granatum* L. (pomegranate) peel or seeds. It is the main phenolic compound responsible for more than 50% of the juice's antioxidant activity. In addition punicalagin has been shown to have antiproliferative efficacy in different cancer types, such as prostate, lung, breast and cervical cancer [49–51]. BCPAP cell line was treated with punicalagin at 25, 50, 100 μM for 24 h and the number and viability of cells decreased following a concentration-dependent pattern. It should be noted that punicalagin induced autophagic cell death, independently of apoptosis and caspase-3 or PARP cleavage [51]. A longer duration of incubation, extended to 72 h, caused a cell cycle arrest at G0/G1 phase and induced senescent growth arrest in human BCPAP cells *via* NF-κB signaling pathway [52]. Another study showed that punicalagin promoted cell death *via* triggering ATM-mediated (ataxia-telangiectasia mutated) DDR (DNA damage response) in human BCPAP cells, which was independent of ROS and DNA conformational change [53]. Pomegranate peel extract rich in punicalagin was evaluated for its anticancer activity in thyroid carcinoma *in vitro* and *in vivo*. Punicalagin potently suppressed proliferation in two thyroid cancer cell lines (BCPAP and TPC-1) and induced cancer cell apoptosis. Punicalagin could also decrease the mitochondrial membrane potential ($\Delta\Psi_m$), indicating that this tannin could induce apoptosis *via* a mitochondria-mediated apoptotic pathway. The authors reported that apoptosis and autophagy were not in contrast, as cell exposure to punicalagin were different [51,53]. To determine the antitumor activity of punicalagin, BCPAP tumor-bearing mice were dosed daily at a dose of 62.5 and 125 mg/kg for a total of 24 days before and after inoculation. Punicalagin significantly inhibited tumor growth in the BCPAP-bearing mice model by reducing cell proliferation and inducing apoptosis [54].

2.1.6. Isoflavones

Isoflavones are 3-phenyl-4H-chromen-4-on derivatives widely found in nature. In plants are found mostly as biologically inactive glycosides: 7-O-β-D-glycosides, 6″-*O*-acetyl-7-O-β-D-glucosides, and 6″-O-malonyl-7-O-β-D-glycosides. They are endowed with chemopreventive and anticancer properties. In addition, they are well-known for their prevention on cardiovascular diseases [55]. It has been reported that a novel isoflavone-derived anti-estrogenic compound, N-t-boc-hexylenediamine derivative of 7-*O*-carboxymethyl daidzein (cD-tboc), could induce apoptosis and retard cell growth in human thyroid cancer cell lines through estrogen receptor β inhibition. This work was performed in *in vitro* human thyroid normal, goiter, and PTC cells [56]. It is known that sorafenib, as mentioned in introduction, can improve progression-free survival in patients with progressive radioactive iodine-refractory DTC, but can cause severe side effects. When evaluating the inhibitory effect of low concentration of sorafenib in combination with cD-tboc and VDM (vitamin D metabolites) in cultured human PTC, the combined treatment inhibited cell proliferation only in the malignant cells. Moreover the drugs association (VDM, cD-tboc, sorafenib 20 μg/mL) inhibited DNA synthesis by 74%, similar (75%) to a generally single concentration of sorafenib 200 μg/mL [57].

Genistein is another isoflavone contained in legumes and soy products with numerous properties, potentially useful in different human diseases, including cancer [58]. Genistein was able to inhibit cell growth in different thyroid cancer cell lines (TPC-1, FTC-133, NPA, FRO, and ARO cells) and to reduce the dedifferentiation markers [24]. In addition, primary PTC cells were treated with genistein (1, 10, 50, 100 μM, for 4 and 24 h), and cell viability, proliferation, DNA and chromosomal damage were evaluated. An anti-proliferative effect was observed at the highest doses of genistein, demonstrating antineoplastic action in primary thyrocytes from PTC [59]. Moreover genistein reduced cell proliferation of primary cells without inducing genotoxic effects in terms of primary DNA damage, showing, instead, a protective action toward oxidative-induced DNA damage [59]. Another study suggested that genistein had anticancer effect in the range of 2.5 to 80 μg/mL in PTC cells (BCPAP, IHH4), through cytoplasmic translocation of β-catenin, thus involving Wnt/β-catenin pathway [60]. Also, down-regulation of cyclin B1 and cyclin A2 was confirmed in both PTC cell lines and normal human thyroid follicular cells. However, decreased expression of cyclin D1 was found in normal thyroid follicular cells, comparing with the up-regulation of cyclin D1 in PTC carcinoma cells. These results suggested that cell proliferation inhibition was mainly through G2/M phase arrest triggered by manipulating the expression of cell cycle regulators. Furthermore, genistein significantly decreased the invasion capacity of PTC cell lines and partially reversed epithelial mesenchymal transition [60]. Isoflavones seemed to have

multiple effects depending both on their biochemical structure and on the thyroid cell line used as model. Nonetheless the increase of apoptosis in different preclinical experiments demonstrated as isoflavones could be a novel potential tool to fight against thyroid cancer.

2.1.7. Glucosinolates

Glucosinolates are sulfur-containing secondary metabolites produced by *Brassicales* species which, upon action of myrosinase enzymes give a very reactive isothiocyanate which is credited to be responsible for the anticancer properties of cruciferous vegetables [61]. Cruciferous vegetables are a rich source of

therapeutic compounds, but paradoxically in thyroid cancer patients are not recommended, presumably due to compounds like phenylisothiocyanates which can block the absorption and use of iodine (and thus inhibition of thyroid hormone synthesis) [62]. The anti-proliferative effects of indole-3-carbinol (I3C) and its acid catalyzed dimer, 3,3′-diindolylmethane (DIM), have been tested on different thyroid cell lines, PTC cells (BCPAP and 8505-C), FTC cells (CGTH-W-1 and ML-1) and primary human goiter cells. DIM possessed anti-cancer effects greater than I3C in both PTC and FTC cells, and induced G1 phase arrest followed by apoptosis activation. In addition DIM showed anti-proliferative properties tissue and cell specific, since in primary culture of goiter cells at 50 μM reduced the number

of viable cells by more than 70% [63]. The authors concluded that synthetic compounds from cruciferous vegetables are available with low toxicity and can be potentially used against thyroid cancer.

2.2. Follicular thyroid cancer models

FTC is the second most common DTC histotype accounting for 10–15% cases [64]. Moreover, FTC has been overshadowed by its more common counterpart - PTC - despite its unique biological behavior and less favorable outcomes [65]. The most common clinical presentation of FTC is a single, painless thyroid nodule. Patients with widely invasive disease usually complain of a palpable neck mass, while patients with minimally invasive disease are usually diagnosed with a palpable neck mass or incidentally diagnosed. Symptoms including hoarseness, dysphagia, neck pressure and also clinical manifestations of thyrotoxicosis have been reported [66]. For convenience and rapid consultation, a table summarized the phytochemicals used in FTC models (Table 2).

2.2.1. Resveratrol

FTC 236 and FTC 238 cell lines treated with resveratrol (1 to 10 μM) showed activation and nuclear translocation of MAPK which was associated with a subsequent increase of p53 and apoptosis [25]. Treatment of FTC236 cells *in vitro* with resveratrol, at doses as low as 5 μM, inhibited tumor cell growth and upregulates Notch1 activity. Interestingly, Notch signaling pathway has been identified as an important signaling cascade that can determinate thyroid cell fate and directly regulate thyroid-specific gene expression [67]. Because 5 μM serum concentrations of resveratrol have been safely achieved in humans, the authors suggested that this compound could be considered as a potential therapy for patients with aggressive, metastatic FTC [68]. Moreover, another work showed that resveratrol strongly activated autophagy in FTC133 and FTC 236. Resveratrol-induced autophagy occurred with an increase in Notch transcript followed by a concentration-dependent inhibition of cellular growth. These findings suggested that growth inhibition by resveratrol (25 μM, 24 h exposure) of human FTC cells could be partially mediated by Notch-induced autophagic flux [69]. It seems that Notch signaling pathway plays a pivotal role in resveratrol effects in FTC cell lines, though more research is needed to expand these data in higher organisms.

2.2.2. Curcumin

Effects of curcumin in cell viability, apoptosis, migration and invasion was evaluated in FTC 133 cell line [70]. Curcumin (20 μM) promoted apoptosis and inhibited FTC133 growth by down-regulation of PI3k/AKT signaling pathway and inhibition of MMP-1, MMP-7 and cyclooxygenase-2 (COX-2). In the same cell line (FTC133) curcumin at 50 μM down-regulated NF-κB expression and induced G2/M phase arrest and caspase 3 activity, with increased mRNA expression of the differentiation genes thyroglobulin (TG) and NIS [34].

2.2.3. Quercetin

In FTC 133 cell line and in other cell lines, TPC-1, NPA, FRO, ARO studied by the authors, quercetin (10, 50, 100 μM) reduced cell

Table 2
Anti-cancer effect of phytochemicals in follicular thyroid cells (FTC).

Phytochemicals	Experimental model	Anti-cancer effects	References
Resveratrol	FTC 236 and FTC 238 cells	• MAPK activation • Produced the MAPK translocation • Increased of p53 • Induced the apoptosis	[19]
	FTC236 cells	• Inhibited the tumor cell growth • Increased the Notch1 activity	[68]
	FTC133 and FTC 236 cells	• Activated the autophagy in human FTC cells • Increased the Notch transcript • Inhibited the cellular growth	[69]
Isoflavones	FTC 133, FTC 236 and FTC 238 cells	• Epidermal growth factor (EGF) enhances proliferation, migration, and invasion of thyroid cancer cells	[70]
	FTC 133 cells	• Neutralized the EGF and TGF-α • Inhibited the growth and invasion of the FTC 133 cell	[71]
		• cD-tboc inhibited growth in primary cultures of FTC cells • cD-tboc induded the apoptosis	[40]
Curcumin	FTC 133 cells	• Promoted the apoptosis • Inhibited FTC133 growthby down-regulation of PI3K/Akt • Inhibited metalloproteinases (MMP-1 and MMP-7) and cyclooxygenase-2 (COX-2)	[72]
	FTC 133 cells	• Induced the arrest of G2/M • Promoted the apoptosis • Inhibited the NF-κB	[27]
Quercetin	FTC 133 cells	• Increased the differentiation marker NIS (sodium iodine symporter) • Decreased the CD97 expression	[21]
Myricetin	FTC 133 cells	• Enhanced the retention of iodine • Increased the influx and decreased the efflux *via* Na^+/I^- symporter	[73,74]
Glucosinolates	CGTH-W-1 and ML-1 cells	• Anti-proliferative effect of DIM • Induced arrested of phase • Induced apoptosis	[44]

proliferation in a concentration-dependent manner [24]. In addition, quercetin increased and induced the differentiation marker NIS while decreasing the expression of the de-differentiation marker CD97.

2.2.4. Myricetin

Myricetin is a natural flavonol compound found in plants, fruits, herbs and wine with anti-tumor, anti-inflammatory and antioxidant properties [71]. Myricetin in FTC 133 cell line enhanced the retention of iodine, increased the influx and decreased the efflux, *via* Na^+/I^- symporter suggesting a therapeutic value of myricetin in the radioiodide treatment of thyroid carcinoma [72,73]. Moreover, myricetin reduced cell viability in a concentration and time-dependent manner, proposing this flavonol as another potential tool to treat FTC.

2.2.5. Isoflavones

In FTC (FTC 133, FTC 236 and FTC 238) and PTC (PTC-UC3) cells, epidermal growth factor (EGF) enhanced proliferation, migration and invasion of differentiated thyroid cancer cells both *in vitro* and nude mice [74]. EGF activation is orchestrated by TGF-α and tyrosine kinase phosphorylation [75]. The tyrosine kinase phosphorylation regulated several protein functions that contributed to the progression of cancer [76]. Genistein, an isoflavone antagonist of tyrosine kinases, has been shown to neutralize the pro-invasion and pro-growth effects of EGF and TGF-α. It inhibited such effects in FTC 133 cell line at concentration of 1 μg/mL [77]. Moreover, daidzein, another isoflavone and its synthetic derivative, cD-tboc, were used in the treatment of various thyroid cancer cell lines. cD-tboc could arrest growth and induce apoptosis through histone-DNA fragments in FTC (MRO 87–1 and WRO) and PTC (NPA) cell lines [78]. Isoflavones are implicated in invasion and migration processes in FTC models, thus they could represent a novel anti-metastatic mean useful in thyroid cancer treatment.

2.2.6. Glucosinolates

In FTC cells (CGTH-W-1 and ML-1), DIM (3,3′-diindolylmethane) was found to be a better anti-proliferative agent than I3C (indole-3-carbinol) resulting in a greater cytotoxic effect at a concentration over three fold lower than predicted by the molar ratio of DIM and I3C as above described [63].

2.3. Anaplastic thyroid cancer

ATC is the less common form of thyroid cancer. Yet, it is one of the most aggressive human neoplasms, with a median survival of less than 6 months after diagnosis and a cancer mortality of 50% [79]. Conventional therapies, chemotherapy, radioiodine, surgery, have been used for ATC patients, without significant reduction of the overall mortality rate. Understanding the biology and natural course of ATC together with the research for new treatment options will lead to a better prognosis and survival of ATC patients. One strategy may be related to the use of phytochemicals, such as terpenoids, alkaloids and phenolic compounds that have been reported for their anti-ATC activity. Table 3 summarized the phytochemicals used in ATC models.

2.3.1. Resveratrol

Resveratrol is known to possess anticancer properties in many cancer types including thyroid cancer. Resveratrol prevents oxidative damage caused by radiolysis of water in thyroid tissues and inhibits chromosomal breaks and DNA damage during radioiodine therapy [80–83]. In addition to its ROS scavenging effect, resveratrol demonstrated anti-thyroid cancer results by activating the Notch1 signaling pathway, which accumulated thyroid-specific differentiation markers and induced re-differentiation [84]. However, drug discovery strategy targeting Notch1 signaling concentration-dependently suppressed ATC cell (HTh7 and 8505C cell lines) growth at 10–50 μM, caused cell cycle arrest at S phase and apoptosis through up-regulation of Notch1, thyroid-specific genes including TTF1, TTF2, Pax8 and sodium iodide symporter (NIS) [85]. Also retinoic acid (RA), a differentiation inducer, in combination with resveratrol 100 μM in THJ-11 T cells, showed a decrease of proliferation activity, associated by increment of nonviable cells and cell death [86]. Resveratrol reversed the RA resistance in ATC cells suggesting a potential use against cancers that evolve retinoic acids-resistance [87]. In addition, resveratrol 100 μM was tested alone in THJ-16T and -21T cell lines where it induced proliferation decrement, cell cycle arrest, apoptosis caspase3-dependent augment [86]. Probably, the most intriguing effect of resveratrol in ATC is its ROS scavenging effect (and the related mechanism of action), a key point that should be deepen and explored particularly when moving to human clinical trials.

2.3.2. Curcumin

Curcumin has a variety of biological activities including anti-ATC effects through down-regulation of NF-κB in BHT-101 cells. Indeed curcumin increased the therapeutic efficacy of docetaxel by apoptosis induction and inhibition of p65 activation and COX-2 expression, promoting the efficacy of radioactive iodine in radiotherapy [84,88]. Moreover, curcumin seemed to adequately enhance the antitumor potency of taxanes in ATC treatment [88]. For instance, curcumin and deguelin, alone or combined inhibited ATC cells growth (CAL-62 cells) [89]. Curcumin reduced the oxidative stress while deguelin enhanced the SOD activity. However the newly identified therapeutic target, CD90, required further investigations in other ATC cell lines and *in vivo* models [89]. Curcumin seems a good adjuvant to standard chemotherapy in ATC. This role should be strongly considered in clinical setting.

2.3.3. Quercetin

Quercetin, like myricetin, increased NIS, a differentiation marker, in FRO cell lines, and decreased the expression of CD97, a de-differentiation marker in ARO cell lines, as reported in the work of Kang and collaborators which analyzed different polyphenols (resveratrol, genistein, quercetin, kaempferol) in PTC, FTC and ATC cell lines [24].

2.3.4. Myricetin

Myricetin showed anticancer properties by apoptosis induction and DNA condensation in SNU-80 cells in a concentration-dependent manner. Myricetin increased sub-G1 phase (suggestive for cell death) and induced activation of caspase cascades and the Bax:Bcl-2 ratio at a concentration of 100 μM and the release of mitochondrial apoptosis-inducing factor (AIF) into the cytosol impairing the mitochondrial membrane potential [90].

2.3.5. Apigenin

Apigenin inhibited FRO cells by promoting apoptosis *via* the elevation of c-Myc levels triggered by p38 and p53 phosphorylation. Interestingly, increased c-Myc acted as a core regulator required for apigenin-induced apoptosis [91]. Moreover apigenin was tested in 8505C and FRO cells finding a decrease in cell viability and phospho-ERK (the extracellular signal-regulated kinase) levels [92]. The authors showed that apigenin associated with PLX4032, an inhibitor of the B-Raf enzyme, augmented the effect of the flavone by cleaved PARP-1 and cleaved caspase-3 elevation. More recently 8505C and CAL62 cell lines were used to evaluate apigenin (10, 20, 30 and 40 μM) with concomitant addition of TRAIL (TNF-related apoptosis-inducing ligand) [93]. Cell viability and Bcl2 protein levels were reduced, while cell death and cleaved PARP increased and phospho-ERK1/2 levels decreased, especially when apigenin was used at 40 μM. Even if apigenin alone or in combination with TRAIL induced cytotoxicity without suppression of AKT, the authors investigated wortmannin (to suppress AKT) and found that this blockade multiplied synergistic cytotoxicity of apigenin with TRAIL. For apigenin see also paragraph 2.3.15.

Table 3
Anti-cancer effect of phytochemicals in anaplastic thyroid cells (ATC).

Phytochemicals	Experimental model	Anti-cancer effects	References
Resveratrol	Thr.C1-PI 33 cells	• Increased cytotoxicity	[81–84]
	HTh7 and 8505C cells	• Cell cycle arrest • Apoptosis induction through upregulation of Notch1, TTF1, TTF2, Pax8 and NIS	[85]
	THJ-16T and THJ-21T cells	• Decreased proliferation • Cell cycle arrest • Apoptosis induction through caspase3-dependent mechanism	[86]
Curcumin	8505C cells	• Cell viability decreased • Apoptosis induction • Blocked p65 activation and COX-2 expression	[87]
	CAL-62 cells	• Suppression of spheroid formation and cellular motility • Cell cycle arrest in G0/G1 phase • Oxidative stress reduction	[88]
Quercetin	FRO and ARO cells	• Decreased proliferation • Augmentation of NIS • Decrease of CD97	[21]
Myricetin	SNU-80 cells	• Apoptosis induction by activation of caspase cascades, modulation of Bax:Bcl-2 ratio, release of mitochondrial apoptosis-inducing factor • Sub-G1 phase accumulation • DNA condensation	[89]
Apigenin	FRO cells	• Apoptosis induction by elevation of c-Myc levels triggered by p38 and p53 phosphorylation	[90]
	8505C and FRO cells	• Cell viability decreased • Phospho-ERK protein levels decreased • Cleaved PARP-1 and cleaved caspase-3 elevation	[91]
	8505C and CAL62 cells	• Cell viability decreased • Bcl2 protein and phospho-ERK1/2 levels decreased • Cleaved PARP levels increased	[92]
Aloperine	8505C and KMH-2 cells	• Cell growth inhibition • Apoptosis induction by caspase-dependent mechanism	[93]
Baicalein	8505C cells	• Apoptosis induction by Bax and caspase-3 activation • Proliferation reduction through VEGF, TGF-β, E-cadherin, N-cadherin, ERK, MAPK protein levels reduction	[94]
Chrysin	HTH7 and KAT18 cells	• Proliferation reduction • Increased Bax:Bcl-2 ratio, cleaved caspase-3, cleaved PARP expression • Decreased cyclin D1, Mcl-1, and XIAP expression	[95]
Deguelin	CAL-62 cells	• Suppression of spheroid formation and cellular motility • Cell cycle arrest in G0/G1 phase	[88]
Epigallocatechin-3-gallate	ARO cells	• Sub-G1 phase accumulation • p21 augmentation • Phosphorylated EGFR, ERK1/2, JNK, and p38 suppression • Apoptosis induction mediated by caspase-3 and cleaved PARP • cyclin B1/CDK1 expression reduction	[96]
Evodiamine	ARO-82-1 cells and xenograft nude mice	• Cell cycle arrest in G2/M phase • Apoptosis induction by caspase-dependent mechanism • Tumor growth inhition • Autophagy induction • Metastatic activities blockade	[97]
	SW1736 cells	• Cell viability reduction • Bcl2 and phospho-AKT protein levels reduction • Apoptosis induction by cleaved PARP, p21, p53, phospho-JNK activation • Phospho-AKT and phospho-NFκB reduction • Cell migration and invasion blockade	[93]
Indirubin	SW1736, HTh7, C643, HTh74, 8305C and 8505C cells	• Cell death induction by a non-classical caspase-independent mechanism	[98]
Thymoquinone	CAL-62 and ACC 448 cells	• Reduced angiogenesis, telomerase activity, cell survival • Increased caspase-3 protein levels (CAL-62 cells) • Increased gene expression of p21 and PTEN (CAL-62 cells) • Decreased gene expression of VEGF-A (CAL-62 cells)	[99]
Triptolide	TA-K cells	• Cell viability reduction • Apoptosis induction by downregulation of p65-NF-κB, Bcl-2 and Bcl-XL (p53-independent mechanism)	[100]
Miscellaneous flavonoid compounds	UCLA RO-81A-1 cells (genistein, luteolin, apigenin, kaempferol, biochanin A)	• Cell proliferation reduction	[101]
	SNU-80 cells (genistein + photofrin)	• Induced production of ROS • Increased expression of pro-apoptotic protein	[102]
	ARO 81–1 cells and mouse xenografts (daidzein derivative)	• Cell proliferation reduction • Histone-DNA fragmentation apoptosis • Tumor volume decrement	[79]

2.3.6. Aloperine

Aloperine is a quinolizidine-type alkaloid isolated from *Sophora alopecuroides L., is traditionally used for the* treatment of numerous diseases, such as infection, heart disorders, rheumatism, gastrointestinal diseases [94]. Aloperine concentration-dependently inhibited cell growth in human ATC cells (8505C and KMH-2) and suppressed *in vitro* tumorigenesis inducing caspase-dependent apoptosis with IC_{50} values of 708.8, 222.0, and 214.4 μM for 8505C cells and 240.8, 221.2, and 208.0 μM for KMH-2 cells considering 24, 48 and 72 h of incubation [4].

2.3.7. Baicalein

Baicalein is a flavone, isolated from the roots of *Scutellaria baicalensis* Georgi and *Scutellaria lateriflora L.* [95] *showing* very interesting properties [96]. The combination of baicalein at 50 or 100 μM with docetaxel 10 nM significantly inhibited proliferation and induced apoptosis in 8505C cells. Moreover, the combination prevented metastasis formation through down-regulation of apoptotic (Bax and caspase-3) and angiogenic protein (vascular endothelial growth factor [VEGF], transforming growth factor β [TGF-β], E-cadherin, and N-cadherin) expression while blocking of ERK, MAPK, AKT, and mammalian target of rapamycin (mTOR) pathways. These results suggested that baicalein could enhance the anticancer effects of docetaxel in ATC [97].

2.3.8. Chrysin

Chrysin is a flavone found in many plants, such as *Oroxylum indicum* (L.) Kurz*, Passiflora caerulea* L., *Passiflora edulis* Sims, *Matricaria chamomilla* L., and in natural products including honey, propolis and *Pleurotus ostreatus* [98]. Chrysin (25–50 μM) dose dependently inhibited proliferation of ATC cells (HTH7 and KAT18) for up to 6 days and showed a significant increase in the ratio of Bax:Bcl-2 expression, cleaved caspase-3, cleaved PARP, along with a decrease in cyclin D1, Myeloid cell leukemia 1 (Mcl-1), and X-linked Inhibitor of Apoptosis Protein (XIAP) [99].

2.3.9. Deguelin

Deguelin is a rotenoid found in the bark, roots and leaves of the *Leguminosae* family. It is known to possess potent chemotherapeutic and chemopreventive potential [100]. Deguelin has showed anticancer efficacies in CAL-62 cells by inducing accumulation of cells in the G0/G1 phase, prompting apoptosis and preventing cell migration [89]. Moreover, deguelin (and curcumin) blocked spheroid formation and cellular motility in matrigel, inducing the authors to suggest that these compounds could be useful in reducing cancer stem-cell phenotype and thus aggressiveness of ATC.

2.3.10. Epigallocatechin-3-gallate

(−)-Epigallocatechin gallate (EGCG), a major catechin in green tea, has been extensively studied for its beneficial health effects and has the potential to impact on a variety of human diseases, including cancer [101]. EGCG was shown to possess remarkable therapeutic potential against the proliferation and apoptosis of ARO cells in a concentration-dependent manner. It also suppressed phosphorylation of EGFR, ERK1/2, JNK, and p38 associated with p21 increment and sub-G1 phase cells accumulation, while activating caspase-3 and cleaved PARP and reducing cyclin B1/CDK1 expression [102].

2.3.11. Evodiamine

(+)-Evodiamine, a major alkaloidal compound of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley [103] and among the most important constituents of the Chinese herb Wu-Chu-Yu, has been demonstrated to possess anti-proliferative effect and inhibition of colonies formation in ARO-82-1 cells throughout cell cycle arrest at G2/M phase [104]. Moreover, evodiamine induced caspase-dependent apoptosis, autophagy and metastatic activities in ATC cells. These effects of evodiamine were further confirmed in a xenograft nude mice model suggesting its therapeutic potential for thyroid cancers [104]. Similarly in SW1736 cells, evodiamine triggered cell viability reduction with Bcl2 and phospho-AKT protein levels decrement [105]. Moreover it induced apoptosis through cleaved PARP, p21, p53, phospho-JNK activation, while decreasing phospho-AKT and phospho-NF-κB. Evodiamine impacted on MMP-2 and MMP-9 reduction and when associated with chemotherapeutic agents (doxorubicin, paclitaxel, cisplatin), it increased cell death rate.

2.3.12. Indirubin

Indirubin, a bis-indole alkaloid, is the active ingredient of Danggui Longhui Wan, a traditional Chinese medicine containing plants such as *Indigofera tinctoria* L. and *Isatis tinctoria* L. [106]. The indirubin derivative 7-bromoindirubin-3′-oxime (7BIO) effectively killed dedifferentiated thyroid carcinoma cells (SW1736, HTh7, C643, HTh74, 8305C and 8505C) by inducing a non-classical caspase-independent cell death and DNA fragmentation. The authors suggested that 7BIO (IC_{50} from 1.54 to 4.32 μM depending on cell type) could represent a new potential therapy for dedifferentiated thyroid cancer, even if the exact molecular mechanism or the type of cell death need yet to be explored [107].

2.3.13. Thymoquinone

Thymoquinone (TQ), or 2-Isopropyl-5-methyl-1, 4-benzoquinone, is a terpene quinone abundant in *Nigella sativa L., is considered a natural remedy for a wide range of diseases, including cancer* [108]. *TQ* reduced angiogenesis, telomerase activity, cell survival and increased pro-apoptotic proteins level in CAL-62 and ACC 448 cells [109]. These effects were mediated by decreased expression levels of human telomerase reverse transcriptase (hTERT), NF-kB and VEGF while phosphatase and tensin homolog (PTEN) and p21 were decreased. Moreover, co-administration of TQ and genistein was more active on ATC cells if compared to FTC cells and could decrease side effects by reducing the amount of drug used in cell treatment [109].

2.3.14. Triptolide

Triptolide, a diterpenoid epoxide, is the major active ingredient of *Tripterygium wilfordii* Hook. f. with various pharmacological activities, including anticancer property [110]. Triptolide exerted concentration-dependent antineoplastic effects in ATC cells (TA-K), by apoptosis induction through p53-independent mechanism which involved NF-κB, thus suggesting triptolite for tumor types with p53 mutation/deletion [111].

2.3.15. Miscellaneous flavonoid compounds

In general, flavonoids such as genistein, luteolin, apigenin, kaempferol, and biochanin A are the most potent inhibitors of thyroid cancer cell lines, UCLA RO-81A-1 (ATC), UCLA NPA-87-1 (PTC), UCLA RO-82W-1 (FTC), with IC_{50} values ranging from 21.7 to 61.31 μM [112]. The inhibitory activity of these flavonoids are mediated *via* the anti-estrogen binding site (AEBS) and/or type II estrogen binding site (EBS). However ATC cells lacked both AEBS and ER, thus the authors suggested that cell proliferation rate could be decreased by flavonoids (especially apigenin and luteolin for ATC cells) with the involvement of other mechanisms of action [112]. Isoflavones such as genistein and daidzein, abundant in legumes, soybeans, lupine, fava bean, kudzu, coffee, are tyrosine kinase, topoisomerase and glycine receptors inhibitors [113,114]. Genistein and photofrin in combination induced cell viability reduction, production of ROS and expression of pro-apoptotic proteins (caspase 3, 8, 9, 12 and cytochrome *c*) in SNU-80 cells [115]. The synthetic derivative of daidzein, cD-tboc, was used in the treatment of various thyroid cancer cells, as previously described. cD-tboc could induce cell apoptosis, but not necrosis in ARO 81–1 cells since histone-DNA fragments were found [56,78]. The cytotoxic effect of cD-tboc was concentration-dependent and modulated by estradiol-17β and caspase inhibitor *Z*-VAD-FMK. Furthermore, cD-tboc significantly decreased

Table 4
Anti-cancer effect of phytochemicals in medullary thyroid cells (MTC).

Phytochemicals	Experimental model	Anti-cancer effects	References
Resveratrol	TT cells	• Decreased proliferation • Apoptosis induction through upregulation of cleaved Caspase 3, PARP, Notch 2 and downregulation of ASCL1 and CgA	[122]
Curcumin analog (EF24)	TT and MZ-CRC-1 cells	• Cell viability reduction • Apoptosis induction through downregulation of phospho-Akt • Increased ROS production	[123]
Combretastatin A-4 phosphate prodrug	TT cells xenograft nude mice	• Tumor volume reduction	[124]
Isoflavones	TT cells	• Cell viability reduction • Increased RET phosphorylation	[125]
Genistein	TT cells	• Scarce cell viability reduction • Scarce apoptosis or DNA synthesis induction	[126]
Carboxy-daidzein-tBoc (cD-tBoc)	TT cells	• Decreased proliferation mediated by ERβ • Apoptosis and necrosis induction • Creatine kinase activity inhibition	[127]
Shikonin	TT cells	• Decreased proliferation • Anti-migration and anti-invasive properties • Apoptosis induction • Decreased proliferation and apoptosis induction (in chorioallantoic membrane TT cells xenograft)	[128]
Withanolides	DRO-81-1 and TT cells	• RET, ERK, and AKT phosphorylation suppression • Tumor volume decrease, growth delay, calcitonin levels decrement (DRO-81-1 cells nude mice xenograft)	[129]
	DRO-81-1 and TT cells	• Decreased proliferation • Cytotoxic effects • Apoptosis induction • RET, mTOR, AKT, p70S6k phosphorylation suppression	[130]

tumor volume and was safe in ATC xenografts mice [78]. cD-tboc seems a good candidate to be explored in human ATC, even if up to now no trials have been attempted.

2.4. Medullary thyroid cancer cell models

MTC is neoplasm that arises from the parafollicular C cells of the thyroid and accounts for 1–2% of thyroid cancers [116]. MTC is frequently aggressive and can metastasize to cervical and mediastinal lymph nodes, liver, lung and bones. Moreover, most of MTCs are sporadic, while 25% of cases are hereditary and are found in multiple endocrine neoplasia (MEN) 2A or 2B syndromes. Germline mutations in the *RET* proto-oncogene (REarranged during Transfection) cause hereditary MTC, while somatic mutations are frequently found in sporadic MTC. Surgery is essentially the only curative treatment for MTC, even if targeted therapy and immunotherapy seem new promising options [117]. There are very limited data on the application of phytotherapeutic compounds for the treatment of MTC. For convenience and rapid consultation, a table summarized the phytochemicals used in MTC models (Table 4).

2.4.1. Resveratrol

Truong et al. unraveled the pro-apoptotic activities of resveratrol in MTC cell line, TT cells. They treated TT cells by increasing concentration of resveratrol and then measured cell proliferation, the expression levels of apoptotic markers (total and cleaved caspase 3 and PARP), MTC markers (Achaete-Scute Complex-Like 1, ASCL1, and chromogranin A, CgA), and Notch 2 [118]. Interestingly they found that resveratrol treatment markedly suppressed proliferation and induced apoptosis by decreasing the expression of ASCL1 and CgA as well as by increasing levels of cleaved caspase 3 and PARP. More interestingly, treating TT cells with this compound significantly augmented Notch 2 levels, suggesting a role for resveratrol in inducing apoptosis through Notch pathway.

2.4.2. Curcumin

Curcumin is a potent agent with different pharmacological activities, including anticancer, anti-inflammatory, antioxidant, antimicrobial activities, which rely on multiple mechanisms of action [119]. However, it has low aqueous solubility which limited its use and led to the development of different strategy to improve its bioavailability [120]. One of this strategy is based on the discovery of novel curcumin derivatives, such as EF24. This molecule was studied in MTC (TT and MZ-CRC-1) cell lines in association with cabozantinib, a small-molecule kinase inhibitor approved for treatment of advanced, progressive MTC, and with ZSTK474, an inhibitor of the PI3k/AKT signaling pathway [121]. The work showed that EF24 alone was effective in reducing cell viability, but its combination with cabozantinib acted in a synergic way increasing the anticancer potential (apoptosis induction and blockade of PI3k/AKT and MAPK signaling pathways) of the approved drug in MTC cell models.

2.4.3. Combretastatin

Combretastatin is one of the most powerful stilbenoid natural product, combretastatin, is a potent anti-angiogenic compound which is a prodrug form of a tubulin-binding compound originally extracted from *Combretum leprosum* Mart. (South African bush willow). As an inhibitor of tubulin polymerization combrestatin is a promising anticancer compound, with reported cytotoxicity in a variety of tumor cells [122]. A study by Nelkin and Ball on mice models of MTC tumors clarified that the combination of combretastatin A-4 phosphate (CA4P) and doxorubicin, considerably delayed the growth of MTC tumor compared to control animals [123].

2.4.4. Isoflavones

Isoflavones are polyphenols that can be found in foods both in free and esterified forms [124]. Genistein is a soy-derived isoflavone and phytoestrogen that has been shown to have antineoplastic properties. For example, Cohen et al. have proven that genistein reduced the proliferative activity of TT cells *in vitro*. They also reported that genistein treatment profoundly hampered the phosphorylation of RET in these cancer cells, thus proposing genistein as a potential TKI [125]. However, Liu et al. have pointed out that genistein had minimal effects on proliferation, apoptosis and synthesis of DNA in TT cell line in comparison to two other TKIs, PP2 and PD098059 [126]. The discrepancy between these two studies may arise from the difference

between the concentrations of genistein. Cohen et al. have treated the TT cells with concentrations of 200 μM, while Liu et al. have used 20 μM genistein. The other isoflavone derivative, cD-tBoc, has been revealed to block cell growth and induce apoptosis and necrosis of TT cell line. Further experiments using an estrogen receptor blocker, PTHPP, provided evidence that anti-proliferative effects of cD-tBoc was mediated by ERβ located in MTC cells [127].

2.4.5. Shikonin

Shikonin is a naphthoquinone, found in the root extract of *Boraginaceae* family, genera *Arnebia, Lithospermum* and *Onosma* [128], and its derivatives have been uncovered to act as anti-proliferative, anti-migration, anti-invasive and pro-apoptotic compounds in TT cells [129]. Moreover, treating chorioallantoic membrane xenografts of TT cells by a single dose of shikonin also confirmed the effect of this agent on apoptosis induction and proliferation suppression.

2.4.6. Withanolides

Withanolides are a group of more than 300 natural steroids and their secondary metabolites. They have several derivatives such as withaferin A (WA) and withanone (WN) and others molecules isolated from *Withania somnifera* (L.) Dunal [130]. Samadi et al. provided both *in vitro* and *in vivo* evidence of anti-tumor activity of WA against MTC tumor and cells. For *in vivo* study, they first injected 5×10^6 DRO-81-1 human MTC-cells into the left posterior neck of experimental mice. After enough growth of the tumor, WA treatment of mice MTC models was initiated for 21 days. Interestingly, all treated mice showed a significant tumor regression, growth delay and calcitonin levels decrement without any unfavorable side effect. In addition, the *in vitro* experiments revealed that WA was a potential TKI through inhibiting the phosphorylation of RET, ERK, and AKT kinases [131]. Two years later, an *in vitro* work of Samadi et al. using MTC cell lines, DRO 81–1 and TT, showed anti-proliferative, cytotoxic and pro-apoptotic activities of some novel withanolides [132]. Furthermore, they demonstrated that the mentioned withanolides selectively prevented RET phosphorylation, AKT/mTOR pathway activation and protein synthesis capacity of MTC cells, suggesting a role in anticancer therapy.

3. Clinical trials using phytochemicals

This paragraph summarized the available clinical trials which used phytochemical agents in human experimentation.

Although several clinical trials have investigated the therapeutic effects of a variety of molecules against thyroid cancers [133–135], there is no remarkable clinical data concerning the application of phytochemicals for the treatment of these tumors. To the best of our knowledge, only few studies have explored the clinical significance of natural products or their derivatives as a therapy for thyroid cancers (Table 5). In a phase I clinical trial CA4P (also known as fosbretabulin) was administered to patients with solid tumors, including two patients with ATC. This study was conducted to evaluate the maximum-tolerated dose, safety, and pharmacokinetic of this compound. After CA4P treatment, two patients died due to cardiovascular complications. However, a 55-year-old man with resistant metastatic ATC showed a complete response. Surgical assessment showed no evidence of micrometastatic residual disease in thyroid gland and the patient has remained disease free for more than 30 months after therapy [136]. These results led to a phase II study to investigate the safety and efficacy of fosbretabulin in 26 ATC patients and evaluated the ability of fosbretabulin in doubling the median survival of patients. Only one patient experienced a near partial remission after two treatment cycles, but rapidly progressed during the third cycle. Fosbretabulin revealed an acceptable safety profile in patients with advanced ATC, but did not elicit significant responses and had no effect on doubling of survival [137]. In another multicenter phase II randomized controlled trial, 80 patients with advanced ATC were enrolled into F + CP arm (fosbretabulin, plus carboplatin and paclitaxel) or the CP arm (carboplatin and paclitaxel). Although median survival in F + CP and CP arms was 5.2 and 4 months, respectively, no significant improvement was seen in progression-free survival between the two arms with the addition of fosbretabulin [138]. A previous randomized and controlled phase I/II trial revealed that thyroidectomy followed by fosbretabulin treatment non significantly increased the survival of the patients [139]. Granata et al., based on available data, concluded that the current knowledge implied acceptable anticancer effect of fosbretabulin in patients with advanced ATC. However, further detailed and comprehensive studies are required to affirm the role of this agent in improving overall survival of ATC patients [140]. The last clinical trial was conducted to determine the effectiveness of curcumin in the form of nanoformulation to prevent genotoxicity effects by radiation after radioiodine therapy in 21 patients with DTC. The genotoxicity index was determined by micronuclei (MN) assay in peripheral blood lymphocytes. The results indicated that curcumin could significantly reduce the amount of MN induced by ^{131}I therapy. Thus, the authors suggested that using curcumin in DTC patients might prevent chromosomal damages induced by ^{131}I [141]. The above mentioned clinical data underscore the necessity to conduct more precise and comprehensive clinical trials using pre-clinically confirmed phytochemicals in thyroid cancer subtypes.

4. Future perspectives and conclusions

Phytotherapeutics are a great source of novel potential compounds useful in thyroid cancer. Resveratrol, genistein, curcumin, and other phytochemicals have been shown to reduce cell proliferation, viability, growth in diverse thyroid cancer cell lines. Moreover, these compounds seemed to be good adjuvant for radioiodine therapy. Still there are unsolved problems related to their bioavailability. Although numerous preclinical experimental data are available, clinical evidence of these phytochemicals in thyroid cancer is scarce and restricted. Therefore, preclinical and more clinical studies are required to unveil the role of phytotherapeutics in the treatment and prevention of thyroid cancer.

Author contributions

All authors contributed to the manuscript. Conceptualization, JSR, RP. Resources, data curation, writing: all authors. Literature review analysis: all authors. Review and editing, GR, GZ, JSR, DA, RP. All the authors read and approved the final manuscript.

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Table 5
Anti-cancer effect of phytochemicals used in clinical trials.

Phytochemicals	Clinical trial	Reported effects	References
Fosbretabulin	Phase I	One out of 25 patient with solid tumor showed a complete response, this patient had a resistant metastatic ATC	[140]
Fosbretabulin	Phase II	One out of 26 patients with ATC had partial remission	[141]
Fosbretabulin, plus carboplatin and paclitaxel	Phase II	80 ATC patients, no significant improvement in progression free survival	[142]
Curcumin	Preclinical	Twenty-one patients with DTC treated with ^{131}I, significant reduced genotoxicity	[143]

Declaration of Competing Interest

The authors declare no conflict of interest.

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