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REVIEW

Phytochemicals in thyroid cancer: analysis of the preclinical studies

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Abstract

Purpose In the search for novel effective compounds to use in thyroid cancer (TC) unresponsive to current treatment, attention has recently focused on plant-derived compounds with anticancer activity. In this review, we discuss the preclinical studies demonstrating phytochemical activity against thyroid cancer cells.

Results/Conclusions In particular, we describe their antiproliferative properties or ability to re-induce iodine retention, thus supporting their potential use as single agents or adjuvants in radioiodine-resistant thyroid cancer treatment.

Keywords Phytochemicals · Thyroid cancer · Combinatory treatment · Preclinical studies

Introduction

The current therapeutic approach to thyroid cancer (TC) is based on the combination of surgery and radioiodine administration. This therapeutic approach has a high success rate in the majority of differentiated TCs able to concentrate radioiodine. However, this approach is not sufficiently effective for tumors with a poorly differentiated phenotype that are unable to concentrate radioiodine [1, 2]. For radioactive iodine (RAI)-refractory tumors, the novel insights provided by molecular investigations have led to novel therapeutics mainly acting as multikinase inhibitors, which are currently being tested as antiproliferation or redifferentiating agents [1, 3, 4]. Some have shown promising results in reducing disease progression and increasing overall survival [5–7], though they can have intolerable side effects, and drug resistance often appears after long treatment [4].

In the search for more effective and well-tolerated agents, increased attention has focused on phytochemicals, chemical compounds with beneficial properties found in the edible part of plants commonly present in our alimentation. Due to their ability to regulate cell proliferation and angiogenesis, some phytochemicals have also shown anticancer activity against many types of neoplastic cells [8, 9]. Since the compounds effective in most tumor cells act against the same molecular targets or signaling pathways altered in TC, some plant-derived compounds have been analyzed in preclinical TC models [10, 11].

In this review, we describe the activity of phytochemicals tested in experimental TC models, either as antiproliferation or redifferentiating agents, by analyzing the data of a selection of articles published in recent years and available on the PubMed and Google Scholar databases. We critically analyze the potential use of phytochemicals as single agents or in combination with other chemotherapeutics in the treatment of RAI-refractory TC.

Phytochemicals with anti-growth activity

Several phytochemicals have demonstrated anti-growth activity in preclinical models of various neoplastic diseases. In this chapter, we summarize the main activities of natural molecules that have been tested as single agents against TC cells.

Resveratrol

Resveratrol is a natural stilbenoid present in grapes, raspberries, blueberries, peanuts, pomegranates, soybeans, and

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red wine [12]. Resveratrol has been shown to have antiproliferative effects in TC cell lines [13], interfering with several molecular mechanisms involved in human tumorigenesis. Growth inhibition of anaplastic TC (ATC) cells was related to cell cycle arrest [14, 15] or apoptotic death associated with modulation of the expression of activated caspase-3, PARP, Notch1, c-fos, and p21 [14–16]. More recently, it has been reported that stilbenoid blocks the proliferation of ATC cells by affecting the STAT3 signaling pathway [17] and follicular TC (FTC) cells in vitro and in vivo by regulating the ST6GAL2-Hippo signaling pathway [18].

Curcumin

Curcumin is a polyphenol present in the rhizomes of *Curcuma Longa L.* that acts on various signaling pathways involved in cellular proliferation [19]. Several studies have described the effects of curcumin on preclinical models of papillary TC (PTC) cells [20, 21]. Cell cycle arrest and apoptotic death were attributed to downregulation of the expression of Bcl-2 and cyclin D1, or p21 and p53 [22–24]. Cell death could be caused by the effect of curcumin on endoplasmic reticulum stress [25]. In addition, in PTC cells, curcumin was able to inhibit cell attachment, spread, migration, invasion [26], and epithelial mesenchymal transition (EMT) by both upregulating the expression of E-cadherin, a molecule that maintains intercellular adhesion integrity, and inactivating matrix metalloproteinase 9 (MMP9), an enzyme able to degrade the basement membrane and extracellular matrix [27, 28]. The inhibition of TC cell invasiveness was also associated with downregulation of the transforming growth factor-β1 (TGF-β1)-smad2/3 signaling pathway [29]. Moreover, curcumin inhibited the migration and invasion of human FTC cells by suppressing the expression and activation of MMP-1/7 through downregulation of the PI3K/Akt signaling pathway [30].

Genistein

Genistein is an isoflavone present in soybeans and soybean products. It has been proposed for the treatment of some neoplasia due to its estrogenic and/or antiestrogenic effects [31, 32]. Recent studies have highlighted the antiproliferative effects of genistein on TC cells through its role as a specific inhibitor of tyrosine kinases (TKi) [33, 34]. Zhang et al. demonstrated that genistein led to cell cycle arrest in the G2/M phase by downregulating cyclin B1 and cyclin A2 and upregulating cyclin D1, which was followed by apoptotic cell death. Furthermore, genistein suppressed EMT cell progression by increasing epithelial E-cadherin and β-catenin expression and decreasing the expression of N-cadherin, vimentin, and the transcription factor Snail [34].

Punicalagin

The phenol punicalagin is contained in pomegranate (*Punica granatum*) and has been proposed as an anticancer agent due to its antioxidant properties [35]. In PTC cells, punicalagin induced senescent growth arrest by triggering NF-κB activation [36], and caused cell death through the autophagy process by activating the MAPK pathway and inhibiting the mTOR signaling pathway [37]. In addition, punicalagin induced human PTC cell death by acting on DNA damage response [38]. Punicalagin was also found to inhibit tumor growth in vivo in TC-bearing mice [39].

Quercetin

Quercetin is a naturally occurring flavone found in a variety of plants, fruits, and vegetables, such as onion, buckwheat, and broccoli, with selective antiproliferative and antitumor effects on many human cancer cell lines [40]. Quercetin treatment of human PTC cells resulted in decreased cell proliferation and an increased rate of apoptosis, the latter related to caspase-3 activation, PARP cleavage, Hsp90 inhibition, and proteasomal degradation [41].

Epigallocatechin gallate

Epigallocatechin-3-gallate (EGCG) is the most abundant and biologically active catechin of green tea. It is widely studied for its anticancer properties [42, 43]. In ATC cells, EGCG inhibited TGF-β1-induced EMT, suppressing migration and invasion properties [44]. Moreover, EGCG reduced growth and induced apoptosis of human ATC cells by suppressing the EGFR/RAS/RAF/MEK/ERK signaling pathway. EGCC also inhibited human thyroid xenograft tumor growth in BALB/c nude mice by inducing apoptosis and downregulating angiogenesis [45].

Baicalein

Baicalein, a bioactive flavone extracted from the root of *Scutellaria baicalensis*, is widely used in nutraceuticals and pharmaceuticals. It has shown inhibitory effects on cell viability, angiogenesis, and inflammation [46]. More recently, it has been reported that baicalein reduced cell viability, arrested the cell cycle, and induced cell death by apoptosis and autophagy by inhibiting ERK and PI3K/Akt pathways in undifferentiated TC cells [47].

Apigenin

The flavone apigenin is abundant in vegetables, fruits, and beverages, such as grapes, apples, chamomile tea, and red wine. Apigenin inhibited PTC cell viability, promoting a

significant accumulation of cells in the G2/M phase via the downregulation of Cdc25C expression. Apigenin led to autophagic cell death as evidenced by Beclin-1 accumulation and LC3 protein conversion [48].

Hydroxytyrosol (HT) and oleuropein (Ole)

HT and Ole are secoiridoids exclusively contained in all *Oleaceae* plant species. HT and Ole represent the majority of bioactive polyphenols in drupes and olive oil [49]. HT and Ole have several biological effects [50, 51], including inhibitory effects on TC cell growth in vitro. In particular, Ole reduced the proliferation of PTC cells by downregulating the phosphorylation levels of Akt and Erk [52], and HT reduced cancer cell viability by promoting apoptotic cell death via the intrinsic pathway [53].

Fosbretabulin and combretastatin A4 (CA4)

Fosbretabulin is a prodrug derived from the African bush willow (*Combretum caffrum*). Its active metabolite, CA4, acts by binding to tubulin and inhibiting microtubule polymerization, resulting in endothelial cell apoptosis. This anti-angiogenetic effect determines tumor necrosis. CA4 inhibited proliferation, migration, and invasion, and promoted TPC-1 cell apoptosis by affecting the PI3K/Akt signaling pathway [54].

Phytochemicals with redifferentiation activity

The loss of ability to concentrate iodide in cancer cells is mainly due to the loss of expression of the sodium–iodide symporter (NIS), as well as of other components of the iodine metabolic machinery. Compounds able to reintroduce the ability to increase TC cell radioiodine concentration are being investigated in various TC preclinical models [5]. In this regard, some plant-derived natural compounds have shown stimulating effects on the expression of genes and proteins involved in iodine metabolism and, in some cases, also on iodide trapping ability.

Curcumin

A radiosensitive effect on TC cells was first described in 2014 [55]. Curcumin showed redifferentiation activity by increasing *thyroglobulin* and *NIS* expression in human TC cell lines from PTC, FTC, and ATC by downregulating NF-kB activity [56]. Recently, Allegri et al. [16] analyzed the effects of some nutraceuticals on the gene expression of various thyroid differentiation markers in two ATC cell lines and found that curcumin induced *NIS* upregulation, making it a potential candidate to overcome chemotherapy and radiotherapy resistance in human TC.

Resveratrol

Resveratrol has been found to be a regulator of *NIS* expression in various TC cells. In an FTC cell line, resveratrol increased cell differentiation by enhancing *NIS* expression [57]. Yu et al. [14] showed that expression of the thyroid-specific genes *TTF1*, *TTF2*, *PAX8*, and *NIS* was upregulated by resveratrol through Notch1 signaling. Recently, resveratrol has also been found to determine an increment in *NIS* and other thyroid-specific genes in ATC cells [16]. Moreover, it has been found to enhance retinoic acid effects on ATC cell line differentiation [15].

Genistein

Genistein administration determined increased NIS expression in FTC cells [57] and an increment in NIS and other thyroid-specific markers in ATC cell lines [16].

Apigenin

The flavonoid apigenin was found to reverse RAI uptake reduction in immortalized PCCL3 rat thyroid cells treated with TGF-β by counteracting TGF-β effect on NIS reduction. This effect was more evident when apigenin was used in combination with Akt, PI3K, and MEK inhibitors [58].

Hesperetin

Hesperetin is a natural flavanone found in citrus fruits. Its antitumor effects have been demonstrated in many cancer preclinical experimental models [59]. Its redifferentiating effects were evaluated on ATC cells by Patel et al. [60] by measuring mRNA levels of thyroid-specific genes. A dose-dependent increase was found in the mRNA levels of TSH receptor and NIS, as well as in the transcription factors TTF1, TTF2, and PAX8, which was associated with the functional activation of the Notch1 signal transduction pathway [60].

Rutin

Rutin is a flavonol widely consumed in a normal diet. It has various pharmacological properties, including antitumor effects [61]. Goncalves et al. [62] demonstrated for the first time that rutin treatment was able to stimulate thyroid iodide uptake in Wistar rats by increasing NIS mRNA and protein levels. In 2018, the same group confirmed these data in vitro in the rat normal thyroid cell line PCCL3. Rutin increased the ability to concentrate iodide intracellularly by increasing

iodide uptake and decreasing iodide efflux, upregulating NIS mRNA and protein expression and increasing NIS translocation to the plasma membrane [63]. These findings, if confirmed in cancer cells, would support rutin as an adjuvant in radioiodine therapy.

Phytochemicals as adjuvants in combination therapy

In view of the clinical use of phytochemicals, preclinical studies were performed to test some natural compounds in association with other anticancer therapeutics. Here we report the most interesting results obtained with combination therapy.

Resveratrol

Bian et al. [64] investigated the antitumor effects of the combined use of resveratrol and rapamycin in two human PTC cell lines. Treatment with both agents significantly decreased cell viability and induced apoptosis more efficiently than cells treated with either compound alone. Invasion and migration capacity were also reduced. In the same work, a mouse xenograft tumor induced with TC cell injection was treated with a combination of resveratrol and rapamycin. The study found that tumor growth rate was attenuated with combined treatment more efficiently than with single treatment. In addition, the phosphorylation of Akt and the mTORC1 target p70S6 kinase was significantly inhibited by combined treatment as compared with rapamycin alone [64].

Curcumin

Some studies have described the effects of curcumin used in combination with other anticancer agents. Curcumin and docetaxel co-treatment reduced the viability of two ATC cell lines compared with separate administration of the two agents, demonstrating that curcumin may lower the concentration of docetaxel required for cell proliferation inhibition. In addition, combination therapy induced the inhibition of NF-kB activation and the downregulation of COX-2 protein expression mediated by docetaxel [65]. The effects of curcumin and TKi sorafenib combined treatment were evaluated in FTC cells. As compared with either treatment alone, a significant increase in the percentage of apoptotic cells, a reduction in invasion and migration properties, and a decrease in p-ERK and p-Akt protein levels were observed. Long-term treatment with curcumin and sorafenib also determined a reduction in cell colony formation [66]. Recently, Khan et al. demonstrated that curcumin enhanced the antiproliferative action of cisplatin in two PTC cell lines. Co-treatment suppressed cell migration by downregulating the expression of matrix metalloproteinases, reduced colony formation, downregulated the JAK/STAT3 pathway, and promoted apoptosis by enhancing the expression of proapoptotic proteins and decreasing expression of antiapoptotic markers [24].

Baicalein

Baicalein was tested in combination with docetaxel in ATC cells by Park et al. [67]. Baicalein enhanced docetaxel-induced apoptosis by increasing the expression of the proapoptotic proteins Bax, caspase-3, and cleaved caspase-3 and inhibiting Bcl-2 expression. Furthermore, the expression of mTOR, ERK, and Akt phosphorylated proteins was significantly reduced with combined treatment compared with untreated cells or docetaxel treatment alone [67].

Quercetin

Combined treatment of PTC cells with sorafenib 0.1 μM and quercetin 25 μM showed a strong inhibiting effect on cell proliferation and a significant reduction in adhesion and migration properties in both cell lines. EMT marker expression was affected by co-treatment, with a synergistic action revealed by an increase in E-cadherin and a decrease in N-cadherin expression [68].

Genistein

Ferrari et al. [33] investigated the effects of co-treatment with genistein and sorafenib in human PTC cells. An antiproliferative effect was induced by the highest doses of genistein, and this effect was synergistically enhanced by co-treatment with sorafenib. Comet assay also demonstrated that this combination did not induce any loss of DNA integrity in PTC cells [33].

Apigenin

The ability of apigenin to restore RAI uptake was more evident when apigenin was used in combination with the PI3K inhibitor GDC-0941. The ability of apigenin to retain RAI was demonstrated in metastatic thyroid cells through increased NIS expression and a decreased rate of iodide efflux [58].

Table 1 summarizes the preclinical studies with combined treatments of phytochemicals and other antitumor compounds.

Phytochemicals in mouse models of thyroid cancer

Only few studies evaluated the impact of phytochemicals on in vivo experimental models of thyroid carcinogenesis.

Table 1 Effects of combining phytochemicals with antitumoral drugs in preclinical models of human thyroid carcinoma

Compounds	Model	Molecular target	References
Baicalein + docetaxel	ATC cells	↓ Bcl-2, mTOR, ERK, p-Akt ↑ Caspase-3, cleaved Caspase-3, Bax	[67]
Curcumin + cisplatin	PTC cells	↑ Caspase-3/9, cleaved Caspase-3/9 ↓ P-CXCR4, MMP9/2; JAK/STAT3	[24]
Curcumin + docetaxel	ATC cells	↓ NF-kB, Cox-2 ↑ cleaved Caspase-3/9	[65]
Curcumin + sorafenib	FTC cells	↓ p-ERK, p-Akt	[66]
Genistein + sorafenib	Primary PTC cells	n.d.	[33]
Quercetin + sorafenib	PTC cells	↓ N-cadherin ↑E-cadherin	[68]
Resveratrol + rapamycin	PTC cells	↑ Caspase-3/8, Bax ↓ Bcl-2, Mcl-1 ↓ p-Akt, p70S6K	[64]

ATC anaplastic thyroid cancer, *Bax* BCL2-associated X protein, *Bcl-2* B-cell lymphoma 2, *Cox-2* cyclooxygenase 2, *ERK* extracellular regulated kinases, *JAK/STAT3* Janus kinase/signal transducer and activator of transcription 3, *Mcl-1* myeloid cell leukemia 1, *MMP9/2* matrix metalloproteinase 9/2, *MTC* medullary thyroid cancer, *mTOR* mammalian target of rapamycin, *NF-kB* nuclear factor kappa B, *n.d.* not described, *p-Akt* phospho-protein kinase B, *P-CXCR4* C-X-C chemokine receptor type 4, *p-ERK* phospho-extracellular regulated kinase, *PTC* papillary thyroid cancer, *p70S6K* p70 ribosomal protein S6 kinase

Table 2 Effects of phytochemicals in thyroid carcinoma xenografts

Compound	Model	Mechanism	References
EGCG	TPC-1 cells in BALB/c nude mice	↓ Ki-67, CD31, p-ERK1/2 ↑ cleaved PARP	[45]
Punicalagin	BCPAP cells in BALB/c nude mice	↑ cleaved Caspase-3 ↓ Ki-67, MMP9	[39]
Resveratrol	KTC-1 and TPC-1 cells in BALB/c nude mice	↓ p-Akt, p70S6K	[64]
	FTC238 cells in athymic nude mice	↑ p-MST1/2, p-LATS1, p-YAP ↓ YAP, TAZ	[18]

BCPAP human papillary thyroid carcinoma, *CD31* cluster of differentiation 31, *EGCG* epigallocatechin-3-gallate, *FTC238* human follicular thyroid carcinoma, *KTC-1* human papillary thyroid carcinoma, *MMP9* matrix metalloproteinase 9, *p-Akt* phospho-protein kinase B, *p-MST1/2* phospho-mammalian sterile 20-like 1/2, *p-ERK1/2* phospho-extracellular regulated kinase 1/2, *p-LATS1* phospho-large tumor suppressor gene 1, *p70S6K* p70 ribosomal protein S6 kinase, *p-YAP* phospho-yes-associated protein, *PARP* poly(ADP-ribose) polymerase, *TAZ* transcriptional co-activator with PDZ-binding motif, *TPC-1* human papillary thyroid carcinoma, *YAP* yes-associated protein

The compounds that were tested also in vivo and their molecular targets involved are reported in Table 2 and discussed below.

EGCG

The administration of EGCG reduced in a dose-dependent manner the growth of human thyroid carcinoma xenograft in BALB/c nude mice accompanied with a reduction of the expression levels of Ki-67, CD31, and p-ERK1/2 and an increase of cleaved PARP [45].

Punicalagin

The anticancer activity of punicalagin in vivo was examined by Li et al. [39] in BALB/c athymic mice. The administration of punicalagin significantly inhibited tumor growth in the BCPAP-bearing mice model by reducing cell proliferation, blocking metastasis and inducing apoptosis. Accordingly, immunohistochemical analysis of the tumors showed a significant reduction of the levels of Ki-67 as well as MMP9 and an increase of cleaved Caspase-3 [39].

Resveratrol

The effects of resveratrol on tumorigenesis of FTC in vivo were investigated by Xu et al. [18] in an athymic nude mouse subcutaneous xenograft model. After resveratrol treatment, tumor tissues showed the activation of the Hippo signaling pathway, as revealed by the modulation of the expression of its several components. In fact, western blotting analysis showed an increase of expression levels of p-MST1/2, p-LATS1, and p-YAP, and a reduction of YAP and TAZ levels [18]. In another work, the effects of resveratrol were evaluated in a mouse xenograft model of cancer originating from the implantation of TC cells. It was observed an inhibition of tumor growth and a reduction of the phosphorylation of Akt and p70S6 kinase [64].

Phytochemicals in clinical trials

In contrast to the abundant preclinical studies showing the anticancer effects of various phytochemicals, only a few clinical studies have been conducted to evaluate the

safety, maximum tolerated dose, and pharmacokinetic characteristics of these compounds before proposing clinical use. In phase I/II clinical trials, administration of several cycles of fosbretabulin, either alone or in combination with carboplatin and paclitaxel, was found to be effective against ATC in a few patients. In 26 patients with advanced ATC, the median survival of seven patients with no disease progression was 12.3 months, and stable disease at 20 months of therapy was observed in one patient. Moreover, one-third of ATC patients survived more than 6 months [69]. In another phase II clinical trial conducted on 80 patients with advanced ATC using doublet carboplatin-paclitaxel chemotherapy with or without fosbretabulin, the 1-year survival of the carboplatin/fosbretabulin arm increased by 17% versus the carboplatin arm, although there was no significant improvement in progression-free survival with the addition of fosbretabulin [70, 71].

Conclusions

Recent molecular studies have led to advancements in defining the alterations occurring in TC pathogenesis, suggesting useful novel molecular biomarkers for early diagnostics, individual management, and targeted therapy [72–75]. However, there is still a need to explore new mild strategies to prevent and treat TCs that are refractory to current treatments. Phytochemicals have received much attention over the last decades as potential sources of chemoprevention and treatment for many tumors, including thyroid neoplasia. The redifferentiation effects of some compounds and the synergistic antitumor action when used in combination with other therapeutics (Table 1) have supported their application as novel potential tools for the treatment of more aggressive thyroid neoplasia. However, although preclinical studies have clearly demonstrated that many phytochemicals have all the characteristics necessary for clinical testing as adjuvants in TC treatment, the mechanisms underlying their anticancer action and their direct molecular targets, necessary to predict an efficient action against human tumors in vivo, have not yet been fully elucidated. In addition, data are lacking on bioavailability, toxicology, and eventual drug resistance. Furthermore, only a few studies have tested their impact in vivo in mice models (Table 2). Finally, since no clinical trials have been conducted to prove their effectiveness on human TCs, further studies on phytochemicals selected by more extensive preclinical studies are necessary before encouraging their clinical use.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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References

1. S. Bulotta, M. Celano, G. Costante, D. Russo, Novel therapeutic options for radioiodine refractory thyroid cancer: re-differentiation and beyond. Curr. Opin. Oncol. **32**, 13–19 (2020)
2. C. Durante, N. Haddy, E. Baudin, S. Leboulleux, D. Hartl, J.P. Travagli, B. Caillou, M. Ricard, J.D. Lumbroso, F. De Vathaire, M. Schlumberger, Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J. Clin. Endocrinol. Metab. **91**, 2892–2899 (2006)
3. S. Wächter, A. Wunderlich, B.H. Greene, S. Roth, M. Elxnat, S.A. Fellinger, F.A. Verburg, M. Luster, D.K. Bartsh, P. Di Fazio, Selumetinib activity in thyroid cancer cells: modulation of sodium iodide symporter and associated miRNAs. Int. J. Mol. Sci. **19**(7), 2077 (2018)
4. M.E. Cabanillas, M. Ryder, C. Jimenez, Targeted therapy for advanced thyroid cancer: kinase inhibitors and beyond. Endocr. Rev. **40**(6), 1573–1604 (2019)
5. S. Bulotta, M. Celano, G. Costante, D. Russo, Emerging strategies for managing differentiated thyroid cancers refractory to radioiodine. Endocrine **52**, 214–221 (2016)
6. G.E. Naoum, M. Morkos, B. Kim, W. Arafat, Novel targeted therapies and immunotherapy for advanced thyroid cancers. Mol. Cancer **17**(1), 51 (2018)
7. A. Jayarangaiah, G. Sidhu, J. Brown, O. Barrett-Campbell, G. Bahtiyar, I. Youssef, S. Arora, S. Skwiersky, S. McFarlane, Therapeutic options for advanced thyroid cancer. Int. J. Clin. Endocrinol. Metab. **5**(1), 26–34 (2019)
8. R. Kotecha, A. Takami, J.L. Espinoza, Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. Oncotarget **7**(32), 52517–52529 (2016)
9. A. Ranjan, S. Ramachandran, N. Gupta, I. Kaushik, S. Wright, S. Srivastava, H. Das, S. Srivastava, S. Prasad, S.K. Srivastava, Role of phytochemicals in cancer prevention. Int. J. Mol. Sci. **20**(20), 4981 (2019)
10. H.J. Shin, K.A. Hwang, K.C. Choi, Antitumor effect of various phytochemicals on diverse types of thyroid cancers. Nutrients **11** (1), 125 (2019)
11. F. Pistollato, M. Masias, P. Agudo, F. Giampieri, M. Battino, Effects of phytochemicals on thyroid function and their possible role in thyroid disease. Ann. N. Y. Acad. **1443**(1), 3–19 (2019)
12. V. Neveu, J. Perez-Jimenez, F. Vos, V. Crespy, L. du Chaffaut, L. Mennen, C. Knox, R. Eisner, J. Cruz, D. Wishart, A. Scalbert, Phenol-explorer: an online comprehensive database on polyphenol contents in foods. Database **2010**, bap024 (2010)
13. A. Rauf, M. Imran, M.S. Butt, M. Nadeem, D.G. Peters, M.S. Mubarak, Resveratrol as an anti-cancer agent: a review. Crit. Rev. Food Sci. Nutr. **58**, 1428–1447 (2018)
14. X.M. Yu, R. Jaskula-Sztul, K. Ahmed, A.D. Harrison, M. Kunnimalaiyaan, H. Chen, Resveratrol induces differentiation markers expression in anaplastic thyroid carcinoma via activation of Notch1 signaling and suppresses cell growth. Mol. Cancer Ther. **12**(7), 1276–1287 (2013)
15. Y.T. Li, X.T. Tian, M.L. Wu, X. Zheng, Q.Y. Kong, X.X. Cheng, G.W. Zhu, J. Liu, H. Li, Resveratrol suppresses the growth and

enhances retinoic acid sensitivity of anaplastic thyroid cancer cells. Int. J. Mol. Sci. **19**(4), 1030 (2018)
16. L. Allegri, F. Rosignolo, C. Mio, S. Filetti, F. Baldan, G. Damante, Effects of nutraceuticals on anaplastic thyroid cancer cells. J. Cancer Res. Clin. Oncol. **144**, 285–294 (2018)
17. J. Wu, Y.T. Li, X.T. Tian, Y.S. Liu, M.L. Wu, P.N. Li, J. Liu, STAT3 signaling statuses determine the fate of resveratrol-treated anaplastic thyroid cancer cells. Cancer Biomark. **27**, 461–469 (2020)
18. G. Xu, J. Chen, J. Wang, J. Xiao, N. Zhang, Y. Chen, H. Yu, G. Wang, Y. Zhao, Resveratrol inhibits the tumorigenesis of follicular thyroid cancer via ST6GAL2-regulated activation of the Hippo signaling pathway. Mol. Ther. Oncolytics **16**, 124–133 (2020)
19. A. Giordano, G. Tommonaro, Curcumin and cancer. Nutrients **11** (10), 2376 (2019)
20. L. Zhang, X. Cheng, Y. Gao, J. Bao, H. Guan, R. Lu, H. Yu, Q. Xu, Y. Sun, Induction of ROS-independent DNA damage by curcumin leads to G2/M cell cycle arrest and apoptosis in human papillary thyroid carcinoma BCPAP cells. Food Funct. **7**, 315–325 (2016)
21. S. Schwertheim, F. Wein, K. Lennartz, K. Worm, K.W. Schmid, Curcumin induces G2/M arrest, apoptosis, NF-kB inhibition, and expression of differentiation genes in thyroid carcinoma cells. J. Cancer Res. Clin. Oncol. **143**(7), 1143–1154 (2017)
22. A. Perna, A.D. Luca, A. Adelfi, L. Pasquale, B. Varriale, T. Esposito, Effects of different extracts of curcumin on TPC1 papillary thyroid cancer cell line. BMC Complement. Altern. Med. **18**(1), 63 (2018)
23. T. Esposito, A. Lucariello, E. Hay, M. Contieri, P. Tammaro, B. Varriale, G. Guerra, A. De Luca, A. Perna, Effects of curcumin and its adjuvant on TPC1 thyroid cell line. Chem. Biol. Interact. **305**, 112–118 (2019).
24. A.Q. Khan, E.I. Ahmed, N. Elareer, H. Fathima, K.S. Prabhu, K. S. Siveen, M. Kulinski, F. Azizi, S. Dermime, A. Ahmad, M. Steinhoff, S. Uddin, Curcumin-mediated apoptotic cell death in papillary thyroid cancer and cancer stem-like cells through targeting of the JAK/STAT3 signaling pathway. Int. J. Mol. Sci. **21** (2), 438 (2020)
25. L. Zhang, X. Cheng, S. Xu, J. Bao, X. Yu, Curcumin induces endoplasmic reticulum stress-associated apoptosis in human papillary thyroid carcinoma BCPAP cells via disruption of intracellular calcium homeostasis. Medicine **97**(24), e11095 (2018)
26. C.Y. Zhang, L. Zhang, H.X. Yu, J.D. Bao, Z. Sun, R.R. Lu, Curcumin inhibits invasion and metastasis in K1 papillary thyroid cancer cells. Food Chem. **139**, 1021–1028 (2013)
27. C.Y. Zhang, L. Zhang, H.X. Yu, J.D. Bao, R.R. Lu, Curcumin inhibits the metastasis of k1 papillary thyroid cancer cells via modulating e-cadherin and matrix metalloproteinase-9 expression. Biotechnol. Lett. **35**, 995–1000 (2013)
28. C. Tan, L. Zhang, X. Cheng, X.F. Lin, R.R. Lu, J.D. Bao, H.X. Yu, Curcumin inhibits hypoxia-induced migration in k1 papillary thyroid cancer cells. Exp. Biol. Med. **240**, 925–935 (2015)
29. L. Zhang, X. Cheng, Y. Gao, C. Zhang, J.D. Bao, X. Guan, H. Yu, R. Lu, Q. Xu, Y. Sun, Curcumin inhibits metastasis in human papillary thyroid carcinoma BCPAP cells via down-regulation of the TGF-beta/Smad2/3 signaling pathway. Exp. Cell. Res. **341**, 157–165 (2016)
30. X. Xu, J. Qin, W. Liu, Curcumin inhibits the invasion of thyroid cancer cells via down-regulation of pi3k/akt signaling pathway. Gene **546**, 226–232 (2014)
31. M. Russo, G.L. Russo, M. Daglia, P.D. Kasi, S. Ravi, S.F. Nabavi, S.M. Nabavi, Understanding genistein in cancer: The "good" and the "bad" effects: a review. Food Chem. **196**, 589–600 (2016)
32. V. Mukund, D. Mukund, V. Sharma, M. Mannarapu, A. Alam, Genistein: Its role in metabolic diseases and cancer. Crit. Rev. Oncol. Hematol. **119**, 13–22 (2017)
33. S.M. Ferrari, A. Antonelli, P. Guidi, M. Bernardeschi, V. Scarcelli, P. Fallahi, G. Frenzilli, Genotoxicity evaluation of the soybean isoflavonegenistein in human papillary thyroid cancer cells. Study of its potential use in thyroid cancer therapy. Nutr. Cancer **71**(8), 1335–1344 (2019)
34. C. Zhang, B. Lv, C. Yi, X. Cui, S. Sui, X. Li, M. Qi, C. Hao, B. Han, Z. Liu, Genistein inhibits human papillary thyroid cancer cell detachment, invasion and metastasis. J. Cancer **10**(3), 737–748 (2019)
35. A.D. Khwairakpam, D. Bordoloi, K.K. Thakur, J. Monisha, F. Arfuso, G. Seth, S. Mishra, A.P. Kumar, A.B. Kunnumakkara, Possible use of *Punica granatum* (Pomegranate) in cancer therapy. Pharmacol. Res. **133**, 53–64 (2018)
36. X. Cheng, X. Yao, S. Xu, J. Pan, H. Yu, J. Bao, H. Guan, R. Lu, L. Zhang, Punicalagin induces senescent growth arrest in human papillary thyroid carcinoma BCPAP cells via NF-kB signaling pathway. Biomed. Pharmacother. **103**, 490–498 (2018)
37. X. Cheng, Y. Gao, X. Yao, H. Yu, J. Bao, H. Guan, Y. Sun, L. Zhang, Punicalagin induces apoptosis-independent autophagic cell death in human papillary thyroid carcinoma BCPAP cells. RSC Adv. **6**(72), 68485–68493 (2016)
38. X. Yao, X. Cheng, L. Zhang, H. Yu, J. Bao, H. Guan, R. Lu, Punicalagin from pomegranate promotes human papillary thyroid carcinoma BCPAP cell death by triggering ATM-mediated DNA damage response. Nutr. Res. **47**, 63–71 (2017)
39. Y. Li, T. Ye, F. Yang, M. Hu, L. Liang, H. He, Z. Li, A. Zeng, Y. Li, Y. Yao, Y. Xie, Z. An, S. Li, *Punica granatum* (pomegranate) peel extract exerts potent antitumor and anti-metastasis activity in thyroid cancer. RSC Adv. **6**(87), 84523–84535 (2016)
40. S.M. Tang, X.T. Deng, J. Zhou, Q.P. Li, X.X. Ge, L. Miao, Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. Biomed. Pharmacother. **121**, 109604 (2020)
41. E. Mutlu Altundağ, T. Kasac, A.M. Yılmaz, B. Karademir, S. Koçtürk, Y. Taga, A.S. Yalçın, Quercetin-induced cell death in human papillary thyroid cancer (B-CPAP) cells. J. Thyroid Res. **2016**, 9843675 (2016)
42. C.S. Yang, H. Wang, Cancer preventive activities of tea catechins. Molecules **21**(12), 1679 (2016)
43. A. Negri, V. Naponelli, F. Rizzi, S. Bettuzzi, Molecular targets of epigallocatechin-gallate (EGCG): a special focus on signal transduction and cancer. Nutrients **10**(12), 1936 (2018)
44. T. Li, N. Zhao, J. Lu, Q. Zhu, X. Liu, F. Hao, X. Jiao, Epigallocatechin gallate (EGCG) suppresses epithelial-Mesenchymal transition (EMT) and invasion in anaplastic thyroid carcinoma cells through blocking of TGF-β1/Smad signaling pathways. Bioengineered **10**(1), 282–291 (2019)
45. D. Wu, Z. Liu, J. Li, Q. Zhang, P. Zhong, T. Teng, M. Chen, Z. Xie, A. Ji, Y. Li, Epigallocatechin-3-gallate inhibits the growth and increases the apoptosis of human thyroid carcinoma cells through suppression of EGFR/RAS/RAF/MEK/ ERK signaling pathway. Cancer Cell Int. **19**, 43 (2019)
46. Y. Gao, S.A. Snyder, J.N. Smith, Y.C. Chen, Anticancer properties of baicalein: a review. Med. Chem. Res. **25**(8), 1515–1523 (2016)
47. M. Wang, S. Qiu, J. Qin, Baicalein induced apoptosis and autophagy of undifferentiated thyroid cancer cells by the ERK/ PI3K/Akt pathway. Am. J. Transl. Res. **11**(6), 3341–3352 (2019)
48. L. Zhang, X. Cheng, Y. Gao, J. Zheng, Q. Xu, Y. Sun, H. Guan, H. Yu, Z. Sun, Apigenin induces autophagic cell death in human papillary thyroid carcinoma BCPAP cells. Food Funct. **6**(11), 3464–3472 (2015)

49. F. Visioli, E. Bernardini, Extra virgin olive oil's polyphenols: biological activities. Curr. Pharm. Des. **17**, 786–804 (2011)
50. S. Bulotta, M. Oliverio, D. Russo, A. Procopio, Chapter 156: Biological activity of oleuropein and its derivatives. in *Natural Products*, eds. by K.G. Ramawat, J.M. Merillon (Springer-Verlag Berlin Heidelberg (2013), p. 3605–3638
51. M. Celano, V. Maggisano, S.M. Lepore, D. Russo, S. Bulotta, Secoiridoids of olive and derivatives as potential coadjuvant drugs in cancer: a critical analysis of experimental studies. Pharmacol. Res. **142**, 77–86 (2019)
52. S. Bulotta, R. Corradino, M. Celano, J. Maiuolo, M. D'Agostino, M. Oliverio, A. Procopio, S. Filetti, D. Russo, Antioxidant and antigrowth action of peracetylated oleuropein in thyroid cancer cells. J. Mol. Endocrinol. **51**(1), 181–189 (2013)
53. G. Toteda, S. Lupinacci, D. Vizza, R. Bonofiglio, E. Perri, M. Bonofiglio, D. Lofaro, A. La Russa, F. Leone, P. Gigliotti, R.A. Cifarelli, A. Perri, High doses of hydroxytyrosol induce apoptosis in papillary and follicular thyroid cancer cell. J. Endocrinol. Invest. **40**(2), 153–162 (2017)
54. W. Liang, Y. Lai, M. Zhu, S. Huang, W. Feng, X. Gu, Combretastatin A4 regulates proliferation, migration, invasion, and apoptosis of thyroid cancer cells via PI3K/Akt signaling pathway. Med. Sci. Monit. **22**, 4911–4917 (2016)
55. S.J. Hosseinimehr, S.A. Hosseini, Radiosensitive effect of curcumin on thyroid cancer cell death induced by radioiodine-131. Interdiscip. Toxicol. **7**, 85–88 (2014)
56. S. Schwertheim, F. Wein, K. Lennartz, K. Worm, K.W. Schmid, S.Y. Sheu-Grabellus, Curcumin induces G2/M arrest, apoptosis, NF-kappaB inhibition, and expression of differentiation genes in thyroid carcinoma cells. J. Cancer Res. Clin. Oncol. **143**, 1143–1154 (2017)
57. H.J. Kang, Y.K. Youn, M.K. Hong, L.S. Kim, Antiproliferation and redifferentiation in thyroid cancer cell lines by polyphenol phytochemicals. J. Korean Med. Sci. **26**, 893–899 (2011)
58. A. Lakshmanan, D. Scarberry, J. Green, X. Zhang, S. Selmi-Ruby, S.M. Jhiang, Modulation of thyroidal radioiodide uptake by oncological pipeline inhibitors and Apigenin. Oncotarget **6**, 31792–31804 (2015)
59. J.M.P. Ferreira de Oliveira, C. Santos, E. Fernandes, Therapeutic potential of hesperidin and its aglycone hesperetin: cell cycle regulation and apoptosis induction in cancer models. Phytomedicine **73**, 152887 (2020)
60. P.N. Patel, X.M. Yu, R. Jaskula-Sztul, H. Chen, Hesperetin activates the Notch1 signaling cascade, causes apoptosis, and induces cellular differentiation in anaplastic thyroid cancer. Ann. Surg. Oncol. **21**(4), 497–504 (2014)
61. L.S. Chua, A review on plant-based rutin extraction methods and its pharmacological activities. Ethnopharmacol **150**(3), 805–817 (2013)
62. C.F.L. Gonçalves, M.C. Santos, M.G. Ginabreda, R.S. Fortunato, D.P. Carvalho, A.C.Freitas Ferreira, Flavonoid rutin increases thyroid iodide uptake in rats. PLoS ONE **8**(9), e73908 (2013).
63. C.F.L. Goncalves, M.L. De Freitas, R.S. Fortunato, L.M. Alves, D. P. Carvalho, A.C. Freitas Ferrera, Rutin scavenges reactive oxygen species, inactivates 5'-adenosine monophosphate-activated protein kinase, and increases sodium-iodide symporter expression in thyroid PCCL3 cells. Thyroid **28**(2), 265–275 (2018)
64. P. Bian, W. Hu, C. Liu, L. Li, Resveratrol potentiates the antitumor effects of rapamycin in papillary thyroid cancer: PI3K/AKT/mTOR pathway involved. Arch. Biochem. Biophys. **689**, 108461 (2020)
65. J.M. Hong, C.S. Park, I.S. Nam-Goong, Y.S. Kim, J.C. Lee, M.W. Han, J.I. Choi, Y.I. Kim, E.S. Kim, Curcumin enhances docetaxel-induced apoptosis of 8505c anaplastic thyroid carcinoma cells. Endocrinol. Metab. **29**, 54–61 (2014)
66. J. Zhang, J. Yu, R. Xie, W. Chen, Y. Lv, Combinatorial anticancer effects of curcumin and sorafenib towards thyroid cancer cells via pi3k/akt and erk pathways. Nat. Prod. Res. **30**, 1858–1861 (2016)
67. C.H. Park, S.E. Han, I.S. Nam-Goong, Y.I. Kim, E.S. Kim, Combined effects of baicalein and docetaxel on apoptosis in 8505c anaplastic thyroid cancer cells via downregulation of the ERK and Akt/mTOR pathways. Endocrinol. Metab. **33**, 121–132 (2018)
68. M. Celano, V. Maggisano, S. Bulotta, L. Allegri, V. Pecce, L. Abballe, G. Damante, D. Russo, Quercetin improves the effects of sorafenib on growth and migration of thyroid cancer cells. Endocrine **67**, 496–498 (2020)
69. C.J. Mooney, G. Nagaiah, P. Fu, J.K. Wasman, M.M. Cooney, P.S. Savvides, J.A. Bokar, A. Dowlati, D. Wang, S.S. Agarwala, S.M. Flick, P.H. Hartman, J.D. Ortiz, P.N. Lavertu, S.C. Remick, A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. Thyroid **19**(3), 233–240 (2009)
70. J.A. Sosa, R. Elisei, B. Jarzab, J. Balkissoon, S.P. Lu, C. Bal, S. Marur, A. Gramza, R.B. Yosef, B. Gitlitz, B.R. Haugen, F. Ondrey, C. Lu, S.M. Karandikar, F. Khuri, L. Licitra, S.C. Remick, Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. Thyroid **24**(2), 232–240 (2014)
71. R. Granata, L.D. Locati, L. Licitra, Fosbretabulin for the treatment of anaplastic thyroid cancer. Future Oncol. **10**(13), 2015–2021 (2014)
72. M. Sponziello, C. Brunelli, A. Verrienti, G. Grani, V. Pecce, L. Abballe, V. Ramundo, G. Damante, D. Russo, C.P. Lombardi, C. Durante, E.D. Rossi, P. Straccia, S. Filetti, Performance of a dual-component molecular assay in cytologically indeterminate thyroid nodules. Endocrine **68**, 468–475 (2020)
73. F. Rosignolo, M. Sponziello, D. Russo, V. Pecce, L. Giacomelli, M. Biffoni, R. Bellantone, C.P. Lombardi, L. Lamartina, G. Grani, C. Durante, S. Filetti, A. Verrienti, Identification of thyroid-associated serum microRNA profiles and their potential use in thyroid cancer follow-up. J. Endocr. Soc. **1**, 3–13 (2017)
74. M. Celano, F. Rosignolo, V. Maggisano, V. Pecce, M. Iannone, D. Russo, S. Bulotta, MicroRNAs as biomarkers in thyroid carcinoma. Int. J. Genomics **2017**, 6496570 (2017)
75. F. Rosignolo, L. Memeo, F. Monzani, C. Colarossi, V. Pecce, A. Verrienti, C. Durante, G. Grani, L. Lamartina, S. Forte, D. Martinetti, D. Giuffrida, D. Russo, F. Basolo, S. Filetti, M. Sponziello, MicroRNA-based molecular classification of papillary thyroid carcinoma. Int. J. Oncol. **50**(5), 1767–1777 (2017)