Cellular and molecular mechanisms of curcumin on thyroid gland disorders

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Abstract:

There is growing literature on the positive therapeutic potentials of curcumin. Curcumin or diferuloylmethane is a polyphenol obtained from the plant *Curcuma longa*. Curcumin has been used widely in Ayurvedic and Chinese medicine for various conditions. The role of curcumin on thyroid glands has been shown by its effects on various biological pathways, including anti-inflammatory, antioxidant, anti-proliferative, apoptosis, angiogenesis, cell cycle and metastasis. We reviewed the recent literature on curcumin applications for thyroid dysfunction, including hyperthyroidism and hypothyroidism, and discussed the molecular mechanisms of these effects. This review aims to summarize the wealth of research related to the thyroid gland therapeutic effect of curcumin.

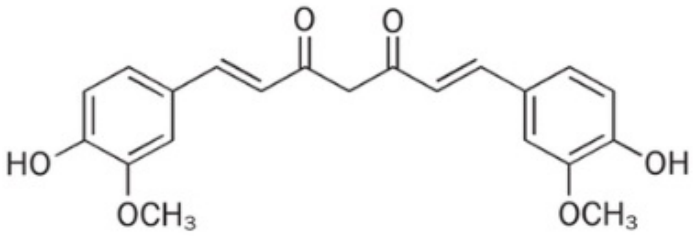
Key Words: Curcumin, Thyroid gland, Molecular mechanisms

Introduction:

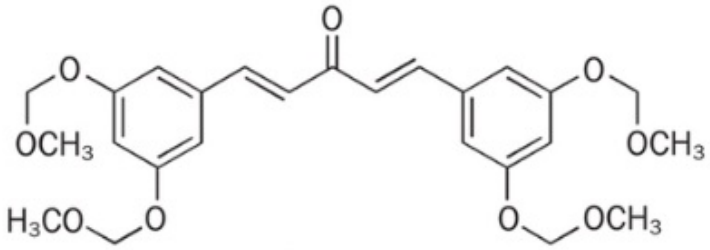
The thyroid gland controls the body metabolism and plays a significant role in human health (1). The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain proper feedback mechanism and homeostasis (2). For T3 and T4 development, iodine is required. The effect of thyroid hormones on body weight and energy intake is also well established (3, 4). Excess thyroid hormone (hyperthyroidism) induces a hypermetabolic condition with higher energy intake and lower weight, decreased cholesterol levels, increased lipolysis and gluconeogénesis (5). In contrast, hypothyroidism is related to hypometabolism as manifested by reduced rest energy, weight gain, hypercholesterolemia, lipolysis, and reduction of gluconeogénesis (6). TH affects the central metabolic pathways that regulate energy balance by controlling energy storage and expenditure (4). TH mainly controls metabolism through skeletal muscle, white and brown fat, brain, pancreas and liver.

Natural products are a valuable source of new lead compounds for treating various diseases, such as metabolic disorders, thyroid disorders and cancers. Several drugs currently used in clinical practice have been found from natural compounds (7). Curcumin (Figure 1A) is the main constituent in the rhizome of *Curcuma longa*. It has a wide range of therapeutic functions and affects many biological processes involved in different diseases (8-21). This review is intended to compile and analyze new findings on the effects of curcumin on thyroid gland diseases and highlight its molecular action mechanism.

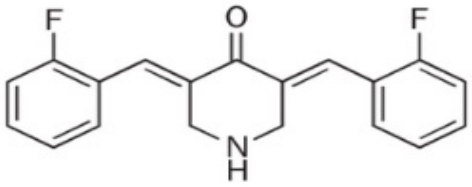
A. Curcumin



B. GO-Y030



C. EF24



Method:

We reviewed literature until February 2021 on the literature on the Knowledge, Medline, Pub Med, Scopus and Google Scholars websites. We used relevant keywords, including thyroid and curcumin. Sixty-two studies have been deemed suitable for this study. Non-English language publications, unpublished articles or abstracts were removed.

In vivo studies

The effects of curcumin

Curcumin effect on the thyroid gland of Wistar rats was evaluated in one study. There was a substantial increase in the proportion of large follicles and decreased free triiodothyronine (FT3) levels in 18-month-old compared to 3-month-long rats by oral administration of curcumin (100 mg/kg). Curcumin also increased FT3 and free thyroxine (FT4) levels in rats aged three months, but the FT3 level decreased considerably in rats aged 18 months. Results showed that curcumin activity depends more on the rat thyroid's functional state that varies with age. The stimulating impact of curcumin on thyroid secretion is more in young rats than in old rats (22).

Curcumin has been studied in the L-thyroxine (T4) mediated hyperthyroidism in rats' cerebral cortex and cerebellum. Treatment with curcumin (30 mg/kg, orally) reduced lipid peroxidation (LPx) level in the cerebral cortex and cerebellum. The translation level of SOD1 and SOD2 and the activity of SOD in the cerebral cortex were significantly reduced by curcumin. Still, the translation level of SOD1 and SOD2 and the activity of SOD in the cerebellum of the rat brain were increased. Elevated tissue LPx level indirectly supports the hypothesis that increased SOD levels in the cerebral cortex of T4-treated rats may be a defensive mechanism to offset increased O_2^- production. In contrast to the cerebral cortex, hyperthyroid rats' cerebellum had lower levels of SOD expression, demonstrating that the enzyme is regulated differently in

different parts of the brain in response to T4 administration. However, supplementing hyperthyroid rats with curcumin improved the expression of SOD1 and SOD2, as well as the activity of total SOD in both brain areas. As a result, we hypothesised that a reduced amount of SOD is expressed in the cerebral cortex of curcumin-supplemented hyperthyroid rats to catalyse the low level of O_2^- to H_2O_2. On the other hand, curcumin improved SOD activity in the cerebellum of T4-treated rats, suggesting that probable regulatory mechanisms in the enzyme production in two separate brain areas are different (23).

The effect of curcumin was evaluated on hypothyroidism induced by propylthiouracil (PTU) in the rat. Curcumin (30 mg/kg, orally) reduced levels of DNA methyltransferases (DNMT1), DNMT3a, DNMT3b, methyl binding domain (MBD4), methyl-CpG-binding protein 2 (MeCP2), p53 and growth arrest and DNA damage-inducible (Gadd45a). Furthermore, curcumin significantly reduced lipid peroxidation and increased hepatocyte nuclei number and sinusoid space in the liver (24).

Treatment with curcumin (12.5 and 50 mg/kg, i.p.) prolonged the survival time of mice when exposed to cryogenic freezing, improved morphology of thyroid in H&E staining, increased levels of FT3 and FT4, up-regulated the expressions of sodium iodide symporter, thyroglobulin and thyroid peroxidase, and down-regulated the expression of thyroid-stimulating hormone receptor (25).

The effect of curcumin on the pituitary–thyroid axis in sodium chlorate (NaClO3) exposure rats was investigated. The administration of curcumin (100 mg/kg, orally) after exposure to NaClO3 reduced TSH and superoxide anion levels, the number of pituitary basophils and caspase-3, increased T3 and T4, and improved thyroid histology (26).

Curcumin (100 mg/kg, orally) reduced TSH level, increased T3 and T4, and improved morphometric parameters on potassium dichromate induced hypothyroidism in the rat (27). In

addition, treatment with curcumin (100 mg/kg, orally) 1 week before and two weeks after exposure to sodium fluoride (NaF) in rats significantly reduced levels of TSH, increased T3 and T4 and restored thyroid histological structure (28).

The combined effect of curcumin with other compounds

The study of vitamin E and curcumin on hyperthyroidism on the rat liver has been shown to decrease serum concentrations T3 and T4, the activity of alanine aminotransferase and aspartate aminotransferase, state 4 respiration of pyruvate/malate (complex I) mediated respiration, as well as mitochondrial lipid peroxidation and mitochondrial protein carbonylation by oral administration of vitamin E (200 mg/kg), and curcumin (30 mg/kg). In addition, a hepatocyte reduction was seen with increased sinus spaces in histological examination of the liver (29).

Orally administration of vitamin E (200 mg/kg) and curcumin (30 mg/kg) on liver antioxidant gene (AOG) expression, including Mn superoxide dismutase (SOD2), Cu/Zn-superoxide dismutase (SOD1), glutathione peroxidase (GPx1), glutathione reductase (GR) and catalase (CAT) in propylthiouracil induced hypothyroid rat for 30 days was shown that combination therapy with curcumin and vitamin E improved CAT, SOD2, GPx1 and GR (30).

Comparison of *Curcuma longa* (*C. longa*) to curcumin in T3-induced oxidative stress and hyperplasia in rat kidney showed that orally administration of *C. longa* and curcumin (30 mg/kg) normalized LPx level and SOD activity in kidney mitochondrial fraction of hyperthyroid rats. Histopathological findings showed that *C. longa* restored tubular dilation and interstitial oedema, whereas curcumin caused hypoplasia. Results suggested that *C. longa* is safer than curcumin in normalizing T3-induced hyperplasia (31).

Orally administration of curcumin (30 mg/kg) and vitamin E (200 mg/kg) significantly increased levels of CAT, GSH and GPx and reduced LPx in the heart of hyperthyroid (induced by T4) and hypothyroid (induced by PTU) rats (32).

In one study, curcumin or quercetin (10 and 20 mg/kg, i.p.) administration 1 week before and two weeks after exposure to NaF in rats significantly increased T3 and T4 serum levels in NaF intoxicated rats (33).

The effects of vitamin E (200 mg/kg) and curcumin (300 mg/kg) in the testis of l-thyroxine (T4) induced hyperthyroid rat showed that treatment with curcumin and vitamin E for 30 days reduced LPx and increased SOD, CAT, GPx, GSH, GSH/ GSSG ratio, hydrogen peroxide (H_2O_2) levels significantly in testicular tissue. Furthermore, serum total T3 and T4 reduced after treatment with curcumin and vitamin E (34).

Orally administration of vitamin E (200 mg/kg) and curcumin (30 mg/kg) on kidney antioxidant enzymes expression in T4 induced hyperthyroid rat for 30 days was indicated that combination therapy reduced LPx and protein carbonylation and increased SOD, CAT, glutathione and ascorbic acid in rat renal cortex (35). The effects of curcumin on the thyroid gland are shown in Table 1.

In vitro studies

The effects of curcumin

Various curcumin concentrations (5, 10 and 25 µg/ml) reduced the percentage of cell survival and increased cell death in thyroid cancer in combination with radioiodine-131 (^{131}I), (36). Furthermore, the effect of curcumin on docetaxel-induced apoptosis of 8505c (human thyroid cancer cell line) anaplastic thyroid carcinoma cells suggests that treatment with varying levels of curcumin (1, 5, 10, 25, or 50 µM) increased cell death, apoptosis and expression of proapoptotic proteins including cleaved caspase-3 and cleaved caspase-9, and reduced the

expression levels of cyclooxygenase-2 (COX-2) and nuclear factor κB (NF-κB) protein in 8505C cells (37).

Treatment of papillary thyroid carcinoma cell (PTC) with different concentrations of curcumin (6.25, 12.5, 25 and 50 μM) inhibited the cell viability, increased the level of intracellular Ca2, upregulated the mRNA expression level of CCAAT/enhancer-binding protein homologous protein (CHOP), as well as induced endoplasmic reticulum (ER) stress by activating transcription factor 6 (ATF6) /X-box binding protein-1 (XBP-1) signaling pathway (38).

In one study, the treatment with curcumin (12.5–50 μM) for 24 h inhibited the growth and proliferation of BCPAP (human thyroid cancer cell line) cells, decreased the mitochondrial membrane potential and the protein level of sarcoplasmic reticulum Ca 2+ ATPase 2, induced apoptosis, the cleavage of caspase-3, -7, and -8, the proteolysis of poly ADP-ribose polymerase and ER expansion, increased phosphorylation of inositol-requiring enzyme-1a and XBP1 mRNA splicing and the level of intracellular Ca2, activated the ATF-CHOP pathway leading to upregulation of pro-apoptotic CHOP expression (39).

Curcumin's effect on different cell lines of human thyroid cancer, including FTC-133 (follicular), TPC-1 (papillary), and BHT-101 (anaplastic), has been studied. Results indicated that curcumin (0, 25, 50 μM) stimulated the expression of the differentiation genes, thyroglobulin (TG) and sodium iodide symporter (NIS) by mRNA expression levels of them, decreased cell proliferation, viability, and the NF-κB p65 activity-induced G2/M arrest and apoptosis, as well as deregulated miRNAs (miR-146b, -181b, -21, -125b, -26a, 200b, 200c, and let7c) involved in tumor progression (40). In addition, results suggested that miR-26a, -125b, -21, -let7c, miR-200c, and -146b play a role in the biological mechanisms of curcumin since they were deregulated by curcumin in thyroid cancer cells. Also, studies have shown that these miRNAs play a role in the NF-κB pathway (40).

Pretreatment with curcumin (12.5, 25, 50 mmol/L) down-regulated the hypoxia-inducible factor 1 (HIF-1) and Bcl-2/adenovirus E1B 19 kDa interacting protein 3 expressions, decreased the generation of ROS, the migration and invasion of K1 cells and the DNA-binding ability to the hypoxia response element (HRE) of HIF-1α, upregulated E-cadherin expression in hypoxia-induced migration in K1 (human thyroid cancer cell line) papillary thyroid cancer cells (41).

Cell viability, migration and invasion and down-regulated expression and activity of matrix metalloproteinase-9 (MMP-9) in K1 papillary thyroid cancer cell lines have been suppressed by curcumin (12.5, 25, and 50 μM), (42).

The effect of curcumin on human papillary thyroid carcinoma cell line has shown that pretreatment with curcumin (12.5, 25, and 50 μM) for 24h reduced cell viability and cell attachment rate, inhibited the spreading of cells on collagen-coated surfaces, the wound-healing migratory, TGF-β1-induced MMPs production and Smad2/3 signaling pathways, up-regulated E-cadherin expression, as well as down-regulated vimentin expression (43).

The protective effect of curcumin (12.5, 25, and 50 μM) for 24h on papillary thyroid cancer K1 cells was evaluated. Curcumin inhibited the cell viability, spreading and migration, the upregulated protein expression level of E-cadherin, and down-regulates the activity and expression of MMP-9 (44).

The effect of various concentrations of curcumin (1-100 μM) load on functionalized with triazolium salts (f-HNT) on human papillary and anaplastic thyroid carcinoma cell lines was showed that curcumin/f-HNT reduced cell viability. The results also suggested that the f-HNT drug carrier system improves curcumin solubility (45).

The combined effect of curcumin with other compounds

It was shown that curcumin (25 μM) and sorafenib (2 μM) had an effect on the proliferation of follicular thyroid cancer cell line (FTC-133) on the thyroid cancer cell line using MTT assay.

In addition, Curcumin and sorafenib therapy decreased the development of cells in the colonies, p-Akt and p-ERK proteins and FTC133 cells invasive and migratory. Furthermore, they increased the total number of apoptotic cells compared to individual treatment (46).

In various cancer cell lines, the inhibitory effect of GO-Y030 (analog of curcumin) (Figure 1B), (3 μM) against NF-κB activation and tumor cell growth were compared with curcumin (30 μM). Following GO-Y030 therapy, activation of NF-κB was suppressed, which was equivalent to curcumin. In addition, there was a direct inhibition of the activity of IKKβ-kinase and suppression of nuclear translocation of the NF-κB p65 subunit. GO-Y030 was also inducing the cell death of a 10-fold lower concentration than that caused by curcumin. The growth-inhibitory effect of GO-Y030 was 4- and 15-fold higher, respectively, compared to curcumin. The GO-Y030, in contrast with curcumin, further decreased the expression of COX-2, c-Myc, cyclin D1 and XIAP. GO-Y030 was considered to be a more than 10-fold inducer of apoptosis compared to curcumin (47).

The effects of curcumin (20 μmol/l) alone and in combination with LY294002 (a PI3K inhibitor), (20 μmol/l) on thyroid cancer cell lines were evaluated. The combination of curcumin and LY294002 significantly reduced tumor cell number, cell viability, promoted apoptosis, and inhibited the adhesion ability, cell migration and invasion rates (48).

The constitutively active RET proto-oncogene is a key factor in developing inherited and sporadic thyroid cancer forms. RET M918T is the most commonly observed mutation in sporadic medullary thyroid carcinoma in approximately 40% of patients. The effect of the XL184 (Cabozantinib), ZSTK474 (an inhibitor of the phosphatidylinositol 3-kinase pathway), and EF24 (a curcumin analog) (Figure 1C), (0.05 to 100 μM), alone and in combination on TT (human medullary thyroid carcinoma cell line) cells carrying a RET C634W mutation, MZCRC-1 (human medullary thyroid carcinoma cell line) cells carrying a RET M918T

mutation, and six human primary thyroid cell lines was examined. Results showed that combinations of XL184+ EF24 and ZSTK474+ EF24 reduced cell viability, ROS production, the protein expression of VEGFR2, phospho-VEGFR2, phospho-ERK, Akt, phospho-Akt, GAPDH, ERK, inhibited cell migration, and induced apoptosis (49).

The effect of curcumin (25 μM) was tested on a papillary thyroid carcinoma cell line, both alone and combined with vitamin E (1 μM) and piperine (200 μM). Following 48 h of incubation, curcumin significantly down-regulated cyclin D, β-catenin, p53, p21, pro-caspase3, Bcl-2 and Bax levels. Curcumin and piperine treatment up-regulated cyclinD and Bax, and down-regulated β-catenin, p53, p21, pro-caspase3, and Bcl-2. Treatment with curcumin and vitamin E up-regulated p21, and Bax, while down-regulated cyclin D, β-catenin, p53, p21, pro-caspase3, and Bcl-2. Results suggested that the effects of curcumin alone were more than with vitamin E and piperin combination (50).

Treatment with extracts of curcumin including Arjuna®, Naturex® and C3Complex® (25 μM) for 24 and 48h on papillary thyroid carcinoma cell line down-regulated cyclinD, β-catenin, pro-caspase3, Nrf2, TNF-α, VEGF, Bcl-2, p21 and p53 (51).

Molecular mechanism

Anti-proliferative action

Curcumin therapy substantially inhibited cell proliferation and viability in thyroid cancer cell lines (40). Curcumin was suggested to have antiproliferative effects through PKC, as many experiments demonstrated its inhibitory effect on the action of protein kinases (52). The signal transduction of these enzymes contributes to the proliferation of thyrocytes. Papillary thyroid cancer cells were treated with curcumin inhibited cell proliferation through inhibition of β-catenin, cyclinD1 and p53 (50). The inhibitory effect of curcumin on cell proliferation was shown by inhibiting the β-catenin pathway and down-regulation of cyclin D1of PTC cells (51).

Curcumin also decreased hyperplasia induced by NaF in the rat thyroid gland (28). Curcumin, in combination with ^{131}I, significantly reduced cell proliferation in thyroid cancer (36).

Anti-inflammatory action

Suppression of inflammation is among the well-documented actions of curcumin and curcuminoids (53-56). Curcumin downregulated NF-κB activity in thyroid cancer cell lines (40). Curcumin has been shown to reduce the number of thyroid infiltrate lymphocytes, the synthesis of IFN-γ, IL-1β, TNF-α, and leukotrienes and inhibited activation of the transcription factor NF-κB which regulates the expression of many inflammatory genes (57, 58). Curcumin has prevented COX-2 and iNOS induction (59). Treatment with 1 lM GO-Y030 also suppressed NF-κB activation in the thyroid cancer cell (47). Curcumin can inhibit the inflammation on the PTC cell line through TNF-α inhibition (51).

Antioxidant action

The mitochondrial transport chain is the primary reactive oxygen species (ROS) source during normal metabolism (60). ROS development from mitochondria has been increased in various conditions, including hyperthyroidism (61-64). Subudhi et al. showed that vitamin E and curcumin scavenge the ROS or reduce ROS production in complex I mediated mitochondrial oxygen consumption in hyperthyroid rats (29). Curcumin and vitamin E administration in hypothyroid rats decreased ROS generation and regulated transcriptional expression of hepatic CAT, GPx1 and GR genes (30). Curcumin is a potent antioxidant that can also pass through the blood-brain barrier without affecting the brain cells (65). Curcumin also reduced HIF-1α in hypoxia-induced migration of K1 cells through inhibition of ROS production (41). Curcumin therapy greatly decreases the transcript and translated products of DNMT1, DNMT3a, DNMT3b, MBD4, MeCP2 and Gadd45a LPx level in the liver of PTU-rat may be attributed to its antioxidative properties (24). There was a decrease in ROS levels after XL184 combined

with EF24 treatment in thyroid cell lines (49). Cell proliferation and cell death could be controlled by *C. longa* and curcumin through modulating cellular oxidant/antioxidant status induced by T3 (31). Administration of curcumin has also inhibited superoxide anion and hydroxyl radical production by preventing the oxidation of Fe^{2+} in Fenton's reaction, which generates •OH radicals (31). Treatment of PTC cells with curcumin displayed antioxidant properties by reducing the TNF-α protein expression (51). Orally administration curcumin reduced superoxide anion in serum of rat exposure to NaClO3 (26). The NRF2 modulation and the ECH associated protein (KEAP 1) functions in rat hearts under altered thyroid states may be related to reducing oxidative stress by vitamin E and curcumin (32). Vitamin E and curcumin therapy protect against oxidative stress on T4 induced hyperthyroid rats primarily through the recovery of antioxidant enzymes such as SOD, CAT, GSH, GPx and LPx (34). The vitamin E and curcumin defense impact T4-induced oxidative stress in rats' renal cortex was reported by modulation of antioxidant enzymes and oxidative stress parameters (35). Orally administration of curcumin (160 mg/day) 3 days before and 7 days after I-131 therapy inhibited oxidative and genotoxic damage (66).

Proapoptotic action

Curcumin is known to modulate apoptosis (67). Analysis of annexin V/PI staining was indicated that curcumin significantly induced apoptosis (40). One of the significant cell survival pathways is the PI3K/Akt pathway. PI3K promotes Akt activation by initial phosphorylation at Thr308 by phosphoinositide-dependent kinase 1 and further phosphorylation at Ser473 by the mammalian target of rapamycin complex 2. Akt signalling plays a vital part in the development of cancer and carcinogenesis. Inactivation of Akt by dephosphorylation plays a crucial role in the suppression of tumors (68). Curcumin induces the apoptosis of FTC133 cells, perhaps through PI3K/Akt and ERK pathways (46). The inhibition of kinases related to survival in the cell cycle regulation has been reported for curcumin (69).

In the human CD4+ T cells (70), human gastric carcinoma cells (71), and human papillary thyroid carcinoma cells, curcumin could induce apoptosis via ER stress (38). The promotion of apoptosis by activating the Ca^{2+}-CaMKII-JNK signaling pathway and activating the ATF-CHOP pathway leading to upregulation of pro-apoptotic CHOP expression in BCPAP cells was enhanced by curcumin (39). By inhibiting sarco-endoplasmic reticulum ATPase 2A (SERCA2) pump, curcumin enhanced intracellular Ca^{2+} influx, bound to calmodulin. The resultant augmentation of calcium/calmodulin-dependent protein kinase II (CaMKII) signaling leads to mitochondrial apoptosis pathway activation (39). Curcumin downregulated NF-κB activity in the thyroid cancer cells, promoting apoptosis and G2/M arrest (40). Song et al. reported that in K1 papillary thyroid cancer cells, curcumin could induce apoptosis via inducing the intracellular ROS formation followed by the collapse of mitochondrial membrane potential (MMP) and the intracellular Ca^{2+} influx, thereby affecting the expression of Bcl-2 and PARP (72). When applied to the thyroid cancer cell line, the combination of curcumin and LY294002 induced higher apoptosis than each agent alone (48). Annexin V-FITC/propidium iodide test results were showed an increase in the fraction of dead cells following EF24+ ZSTK474 treatment in the thyroid cancer cell line (49). Curcumin treated hyperthyroid animals reduced ROS production could be the causative factor for reducing T3-induced hyperplasia to below normal level by induction of apoptosis (31). Papillary thyroid cancer cells were treated with curcumin-induced apoptosis through reduction expression levels of BAX, pro-caspase3 and Bcl-2 (50).

Anti-metastasis action

Curcumin could inhibit tumor progression by deregulation of miRs (40). Curcumin also inhibited hypoxia-induced K1 cell migration and invasion (41, 42). Curcumin inhibited the invasion and metastasis of papillary thyroid cancer cells by suppressing the TGF-β/Smad2/3 pathway (43). Analyses of zymography and PCR indicated that curcumin inhibited metastasis

in BCPAP cells by suppressing the TGF-β/Smad2/3 pathway and targeting the expression of MMP-2 and MMP-9 (43). In addition, curcumin demonstrated epithelial-mesenchymal transition (EMT) inhibition through the restitution of the expression of epithelial marker E-cadherin and weakening mesenchymal marker vimentin expression (43). The previous study's findings also indicated that curcumin inhibits NF-κB activation and suppresses NF-κB-regulated gene products involved in the process of metastasis (73). In human thyroid cancer cell lines, curcumin suppressed cell adhesion, migration, and invasion by inhibiting PI3K and Akt signaling pathways (48). Curcumin could inhibit invasion and metastasis of thyroid cancer cells through up-regulating E-cadherin expression and down-regulating activity and protein level of MMP-9 (44). Furthermore, curcumin could suppress both the EMT of K1 cells and cell migration (44).

Angiogenesis action

COX-2 plays an essential role in the progression of tumors by augmenting angiogenesis and cell growth (74). COX-2 is overregulated in thyroid cancer that can suppress apoptosis but increase angiogenesis and cell invasion. The COX-2 expression was inhibited in 8505C cells by curcumin treatment (37). Curcumin could inhibit angiogenesis of the papillary thyroid cell by the down-regulation VEGF expression level (51).

Cell cycle

Analysis of cell cycles showed that curcumin induced arrest in thyroid cancer cells for step G2/M (40). Curcumin therapy-induced cell cycle arrest in G0/G1 phase. It inhibited thyroid carcinoma cell growth by inhibiting DNA replication and protein synthesis and disrupting the thyroid carcinoma cell cycle (48). Curcumin can inhibit the progression of the cell cycle by inhibiting cyclin D1 protein (50). Figure 2 presents the mechanism of the action of curcumin on the thyroid gland.

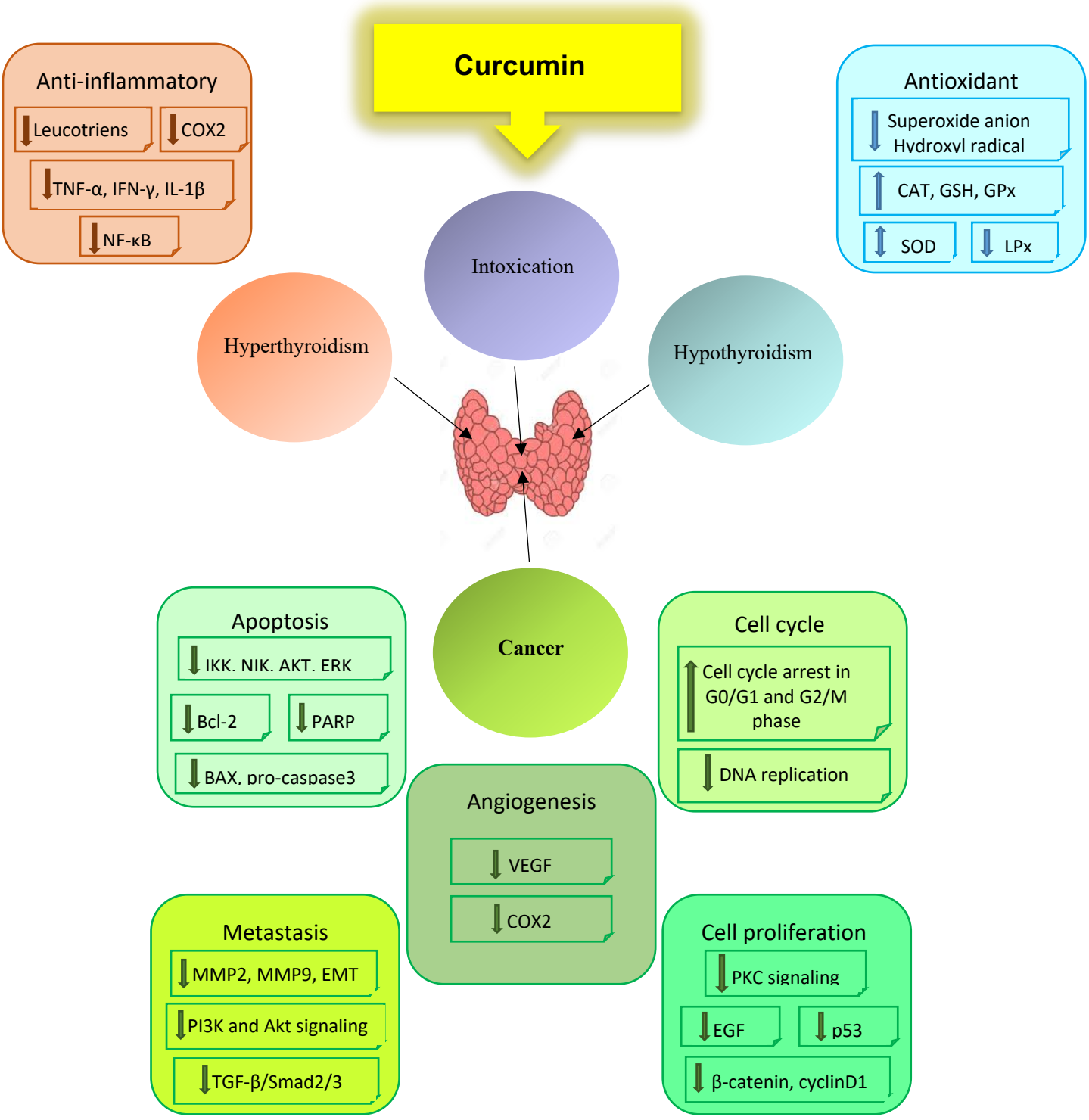


Figure 2. Mechanisms of action of curcumin on the thyroid gland.

Side effects of curcumin

Curcumin has a long history of being safe. Curcumin's Allowable Daily Intake (ADI) value is 0–3 mg/kg body weight, according to JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) studies (75). Curcumin's safety and efficacy have been proven in several studies on healthy people. Despite the fact that the drug's safety has been verified, several negative side effects have been documented. In a dosage response trial, seven participants who received 500–12,000 mg and were observed for 72 hours had diarrhoea, headache, rash, and yellow stool (76). In another trial, some people who took 0.45 to 3.6 g of curcumin every day for one to four months had nausea and diarrhoea, as well as an elevation in serum alkaline phosphatase and lactate dehydrogenase levels (77). Using an ethanol-induced ulcer model in Wistar rats, the pharmacological interactions of a turmeric acetone extract (TAE) and curcumin with popular anti-ulcer medications (ranitidine and bismuth subsalicylate) were examined. TAE and curcumin in combination with bismuth subsalicylate demonstrated an additive association, indicating that there is no pharmacological interaction. When turmeric or curcumin was given at least 15 minutes after ranitidine, the gastroprotective effect of ranitidine was not affected (78).

Conclusion

In this review article, the role of curcumin in various cell model types and mechanisms underlying the therapeutic effects of curcumin on different aspects of thyroid gland problems, such as hypothyroidism, hyperthyroidism and cancer, are addressed. Curcumin has therapeutic potential, including anti-inflammatory, anti-oxidant and anti-neoplastic activities. However, further experimental and clinical studies are warranted to explore the exact mechanism of action and the clinical applications of this effect more clearly.

CONSENT FOR PUBLICATION
Not applicable.
FUNDING

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CONFLICT OF INTEREST:

The authors declare no conflicts of interest.

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None.

Table 1. Summary of studies reporting the effects of curcumin on the thyroid gland.

	Therapy	Exp. model	Effect	Ref.
In vivo	Curcumin (100 mg/kg), orally	Healthy male Wistar rats	Stimulated thyroid hormone secretion in young rats	(22)
	Curcumin (30 mg/kg), vitamin E (200 mg/kg), orally	L-thyroxine induced hyperthyroidism in rat	Protective effect on hepatic dysfunction and oxidative stress	(29)
	Curcumin (30 mg/kg) + vitamin E (200 mg/kg), orally	PTU-induced hypothyroid rats	Improved AOG expression	(30)
	Curcumin (30 mg/kg), orally	L-thyroxine induced hyperthyroidism in rat	Reduced LPx level, SOD1 and SOD2 translation, and SOD activity in cerebral cortex and increased activity in cerebellum.	(23)
	Curcumin (30 mg/kg), orally	PTU-induced hypothyroid rats	Improved histopathological and epigenetic changes in liver injury	(24)
	Curcumin (12.5 and 50 mg/kg), i.p.	Mice exposed to cryogenic freezing	Prolonged the survival time of the cryogenic freezing mice	(25)
	Curcumin and *C. longa* (30 mg/kg), orally	L-thyroxine induced hyperthyroidism in rat	Normalized LPx level and SOD activity in hyperthyroid rats	(31)
	Curcumin (100 mg/kg), orally	Rat exposure to NaClO3	Increased T3 & T4 Reduced TSH and superoxide anion	(26)
	Curcumin (100 mg/kg), orally	Potassium dichromate induced hypothyroidism in rat	Protective effect against hypothyroidism and thyroid tissue damage	(27)
	Curcumin (30 mg/kg), vitamin E (200 mg/kg), orally	PTU-induced hypothyroid rats T4 induced hyperthyroid rat	Increased levels of CAT, GSH and GPx Reduced LPx in heart tissue	(32)
	Curcumin (100 mg/kg), orally	Rat exposure to NaF	Reduced TSH Improved histological changes	(28)
	Curcumin or quercetin (10 and 20 mg/kg), i.p.	Rat exposure to NaF	Increased T3 and T4	(33)
	Curcumin (30 mg/kg), vitamin E (200 mg/kg), orally	L-thyroxine induced hyperthyroidism in rat	Reduced LPx, T3 and T4 Increased SOD, CAT, GPx, GSH, GSH/ GSSG, H_2O_2	(34)
	Curcumin (30 mg/kg), vitamin E (200 mg/kg), orally	L-thyroxine induced hyperthyroidism in rat	Reduced LPx and protein carbonylation Increased SOD, CAT, glutathione and ascorbic acid	(35)

In vitro	Curcumin (5, 10 and 25 μg/ml), ^{131}I (100 μl), *in vitro*	Thyroid cancer cell	Reduced the percentage of cell survival Increased cell death	(36)
	Curcumin (25 μM), sorafenib (2 μM), *in vitro*	FTC133 cell line	Synergetic anti-neoplastic effect (sorafenib and curcumin)	(46)
	Curcumin (30 μM) and GO-Y030 (3 μM), *in vitro*	PC3, PK-1, SW620, 8505c, SH-10-TC, MCF7 and HuCCT-1 cell lines	Inhibited IKKβ Suppresses NF-κB signaling Induced apoptosis	(47)
	Curcumin (1, 5, 10, 25, or 50 μM), *in vitro*	Docetaxel-induced apoptosis in 8505C and CAL62 cell lines	Inhibited cell proliferation and increased apoptosis	(37)
	Curcumin (6.25, 12.5, 25 and 50 mM), *in vitro*	BCPAP cell line	Suppressed cell viability of BCPAP cells	(38)
	Curcumin (12.5–50 uM), *in vitro*	BCPAP cell line	Inhibited thyroid cancer cell growth through ER stress-associated apoptosis	(39)
	Curcumin (0, 25, 50 μM), *in vitro*	TPC-1, BHT-101 FTC-133 cell lines	Inhibited the growth of thyroid cancer cells	(40)
	Curcumin (12.5, 25, 50 mmol/L), *in vitro*	Hypoxia-induced migration in K1 PTC	Decreases expression of HIF-1α	(41)
	Curcumin (12.5, 25, 50 μM), *in vitro*	K1 PTC cell line	Suppressed cell viability, migration and invasion	(42)
	Curcumin (12.5, 25 and 50 μM), *in vitro*	BCPAP cell line	Anti-metastatic and anti-EMT activities	(43)
	Curcumin + LY294002 (20 μmol/l), *in vitro*	FTC133 cell line	Inhibited phosphorylation of PI3K and Akt signaling pathways, growth, cell migration and invasion Promoted apoptosis Attenuated MMP1/7 and COX-2 expressions	(48)
	Curcumin (12.5, 25, 50 μM), *in vitro*	K1 PTC cell line	Inhibits metastasis via modulating E-cadherin and MMP9	(44)
	Curcumin load into f-HNT (1-100 μM), *in vitro*	BCPAP, SW1736, 8505 C and C643 cell lines	Cytotoxic effects against thyroid cancer cell lines	(45)
	XL184, ZSTK474 and EF24 (0.05 to 100 μM), *in vitro*	TT and MZCRC-1 cell lines	Inhibited cell migration Induced apoptosis	(49)
	Curcumin (25 μM), piperine (1 μM) and vitamin E (200 μM), *in vitro*	PTC cell line	Inhibitory effect on cell proliferation, β-catenin and p53	(50)
	Arjuna®, Naturex® and C3Complex® (25 μM), *in vitro*	PTC cell line	Induced apoptosis Inhibited cell proliferation	(51)

Abbreviations: GO-Y030: Analog of curcumin, PTU: propylthiouracil, AOG: antioxidant gene, LPx: Lipid peroxidation, HIF-1α: EMT: epithelial–mesenchymal transition, LY294002: a PI3K

inhibitor, MMP9: matrix metalloproteinase-9, f-HNT: functionalized with triazolium salts, XL184: Cabozantinib, ZSTK474: inhibitor of the PI3-kinase signaling pathway, EF24: a curcumin analog, i.p.: Intrapritoneally, *C. longa*: curcuma longa, PTC: papillary thyroid carcinoma, NaClO3: sodium chlorate, NaF: sodium fluoride, H_2O_2: hydrogen peroxide, ^{131}I: radioiodine-131,

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