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Nutritional Sources and Anticancer Potential of Phenethyl Isothiocyanate: Molecular Mechanisms and Therapeutic Insights

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Phenethyl isothiocyanate (PEITC), a compound derived from cruciferous vegetables, has garnered attention for its anticancer properties. This review synthesizes existing research on PEITC, focusing on its mechanisms of action in combatting cancer. PEITC has been found to be effective against various cancer types, such as breast, prostate, lung, colon, and pancreatic cancers. Its anticancer activities are mediated through several mechanisms, including the induction of apoptosis (programmed cell death), inhibition of cell proliferation, suppression of angiogenesis (formation of new blood vessels that feed tumors), and reduction of metastasis (spread of cancer cells to new areas). PEITC targets crucial cellular signaling pathways involved in cancer progression, notably the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), Protein Kinase B (Akt), and Mitogen-Activated Protein Kinase (MAPK) pathways. These findings suggest PEITC's potential as a therapeutic agent against cancer. However, further research is necessary to determine the optimal dosage, understand its bioavailability, and assess potential side effects. This will be crucial for developing PEITC-based treatments that are both effective and safe for clinical use in cancer therapy.

1. Introduction

Phenethyl isothiocyanate (PEITC) is a naturally occurring compound identified in cruciferous plants belonging to the family Cruciferae.[1] PEITC is a common aromatic isothiocyanate compound related to sulforaphane.[1,2] Enzymatic hydrolysis of sulfur and nitrogen in glucosinolates (GSLs) by the action of the myrosinase enzyme is responsible for releasing the PEITC.[2,3] Besides, the hydrolysis of GSLs compounds and the production of PEITC are considered crucial defense mechanisms against climate change, stress, and even pathogens such as insects, bacteria, and fungi.[2] PEITC possesses significant bioactive properties such as anti-inflammatory, antioxidant, antimicrobial, and anticancer activity.[4] Among all the biological importance of PEITC,

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the antitumor activity has received significant attention due to its powerful chemopreventive and cancer-killing mechanisms.[5] PEITC (C_9H_9NS) is one of the most abundant isothiocyanate products characterized by a phenethyl radical linked to a nitrogen atom.[2] PEITC has a low molecular weight of 163.2 g mol^{-1}, and it is considered a reactive compound as it is a highly electrophilic molecule with a hydrophobic nature ($\log P = 3.47$); thus, it has a susceptibility to a nucleophilic attack, particularly at the central carbon that is electron deficient.[5] All the isothiocyanates are not found in nature in their known form. Instead, they are produced when GSLs, stable thioester compounds, are hydrolyzed by the action of the myrosinase enzyme.[6,7] Nature is a rich source of medicinal products and bioactive compounds, widely used to treat several diseases, including cancer.[8] About 74.8% of the currently used anticancer drugs are from natural sources.[6,9] PEITC shows remarkable potential in cancer treatment and prevention because it can target several proteins that block multiple cancer-initiation mechanisms, such as metastasis and cellular proliferation (by inducing apoptosis along with cell cycle arrest), making PEITC effective in preventing cancer initiation processes.[6] PEITC is a promising anticancer agent whose effect extends to various cancers such as leukemia, breast, lung, prostate, colon, and gastric cancers.[4] Isothiocyanates have been widely used for traditional purposes; plants from the family Brassicaceae, for example, have been utilized as green manures to get rid of weeds and enhance the quality of the crops due to their antimicrobial and insect-repellant activity.[10] Moringa's leaf extract has several traditional uses as it is applied to the skin to treat skin rashes, wound healing, convulsions, and paralysis.[11] In addition, its seeds were efficient in water purification. Likewise, they were chewed to treat abdominal pain and symptoms related to diabetes, such as hyperglycemia.[12] Furthermore, all parts of Moringa have been traditionally used as anti-inflammatory, antioxidant, anticancer, hypotensive, and antibacterial agents.[13] Folk uses of the Horseradish herb possess several advantages; it treats ailments like anemia, bronchitis, gastritis, sinusitis, and rheumatism.[14] This plant's syrup has traditionally been used for its pungency as a cough sedative when mixed with licorice.[14] GSLs, the precursors of ITCs, are distributed in all plant parts, such as leaves, roots, seeds, and stems. The highest concentration of GSLs is found in the youngest plant tissue, which decreases as the plant matures due to the degradation of sulfur to meet its sulfur demand.[15] Different types of ITCs are produced by the hydrolysis of GSLs in vegetables from the Brassicaceae family and related families.[7] This family comprises about 3200 plant species, including common plants such as horseradish, mustard, cabbage, broccoli, cauliflower, and rapeseed.[7,15] Several in vitro models demonstrate the anticancer properties of PEITC due to the ability to suppress angiogenesis, which is the formation of new blood vessels from pre-existing ones.[16] The process of angiogenesis plays a crucial role in cancer development, providing the necessary blood supply for cancerous tissues. Therefore, the anti-angiogenic activity of PEITC is critical to inhibiting cancer development.[16,17] The effect of PEITC on the expression of hypoxia-inducible factors (HIF-1) and vascular endothelial growth factor (VEGF) under hypoxic conditions (1% oxygen level) was investigated in various cancer cell lines, including colon, prostate, breast, and liver cancer.[17] PEITC showed a remarkable ability to suppress HIF-1 and VEGF in these cancer types under hypoxia.[17,18]

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2. Methodology

This study aimed to provide a comprehensive overview of the current knowledge regarding the potential anticancer effects of PEITC and the mechanisms underlying these effects. We performed an extensive literature search using various electronic databases such as PubMed/MedLine, Google Scholar, Scopus, Web of Science, EMBASE, and Cochrane Library. The keywords for the search strategy: "Phenethyl Isothiocyanate," "PEITC," "Anticancer," "Cancer," "Cellular Mechanisms," and "Molecular Mechanisms" were used in different combinations using Boolean operators (AND, OR) to ensure an extensive search. The study included original research articles, both in vivo and in vitro studies, and clinical trials reporting on the anticancer effects of PEITC and their mechanisms of action. Reviews, commentaries, editorials, and articles not written in English were excluded. All identified studies were screened by title and abstract for relevance, and the full texts of potential studies were further examined for eligibility. For each included study, the following data was extracted: first author's name, publication year, type of cancer studied, model used (in vivo, in vitro, or clinical study), PEITC concentration used, anticancer effects observed, and the underlying mechanisms identified. A narrative synthesis of the findings was performed; due to the heterogeneity in the types of cancer, models used, and outcomes reported among studies, a meta-analysis was not feasible. The molecular and cellular pathways implicated in the antitumor effects of PEITC were analyzed and categorized based on common themes and pathways. We also manually searched the reference lists of retrieved articles and relevant reviews to identify potential additional studies that may still need to be identified in the database search. The most representative data have been included and summarized in tables and figures. The taxonomy of the plant has been validated according to WorldFloraOnline, and chemical structures according to PubChem.[19,20]

3. Phenethyl Isothiocyanate: General Characterization

3.1. Natural Sources

Isothiocyanates (ITCs) are the most common products that result from the enzymatic breakdown of GSLs by myrosinase

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Table 1. 2-Phenylethyl glucosinolate (gluconasturtiin) distribution among plants of the family Brassicaceae.

Plant	Plant part	Origin	Conc. of GNST	Reference
Nasturtium officinalis R. Br. (watercress)	Seeds	Pakistan	12.60 mmol g^{-1}	[29]
	Seeds	Seoul, Korea	0.13 μmol g^{-1} DW	[30]
	Flowers		0.17 μmol g^{-1} DW	
	Leaves		0.08 μmol g^{-1} DW	
	Stems		0.06 μmol g^{-1} DW	
	Roots		0.02 μmol g^{-1} DW	
	Whole plant	Sabah, Malaysia	0.47 μmol g^{-1} FW	[31]
	Aerial parts with flowers	Cracow, Poland	15.11 μmol g^{-1} DW	[32]
Barbarea verna (Miller) Asch. (upland cress)	Seeds	Spain	6.4 mmol g^{-1}	[29]
	Seeds	Ontario, Canada	104 μmol g^{-1}	[33]
Leavenworthia alabamica Rollins (Alabama gladecress)	Seeds	Unknown	4.7 mmol g^{-1}	[29]
Leavenworthia torulosa Gray (necklace gladecress)	Seeds	Tennesseee, USA	2.6 mmol g^{-1}	[29]
Rorippa indica (L.) Hiem (variableleaf yellowcress)	Seeds	India	10.9 mmol g^{-1}	
Selenia grandis R. F. Martin (large selenia)	Seeds	Texas, USA	3 mmol g^{-1}	
Selenia aurea Nutt. (golden selenia)	Seeds	Unknown	2.50 mmol g^{-1}	
Brassica oleracea var. *botrytis* (cauliflower)	Edible tissues	New York, USA	0.4 μmol g^{-1} DW*	[34]
	Sprouts	Kyoto, Japan	0.30 μmol g^{-1} DW	[35]
	Shoots		0.81 μmol g^{-1} DW	
	Roots		52.08 μmol g^{-1} DW	
Brassica oleracea var. *italica* (broccoli)	Edible tissues	New York, USA	0.4 μmol g^{-1} DW*	[34]
	Seeds	Kyoto, Japan	2.03 μmol g^{-1} DW	[35]
	Sprouts	Kyoto, Japan	4.05 μmol g^{-1} DW	[34]
	Shoot	Kyoto, Japan	1.20 μmol g^{-1} DW	[35]
	Roots	Kyoto, Japan	34.35 μmol g^{-1} DW	[36]
Brassica oleracea var. *gemmifera* (Brussels sprouts)	Edible tissues	New York, USA	0.5 μmol g^{-1} DW*	[37]

GNST: Gluconasturtiin; USA: United States of America; DW: Dry weight; FW: Fresh weight.

(*β*-thioglucosidase) enzyme.[21,22] These compounds come from cruciferous plants (Brassicaceae), such as watercress, cabbage, cauliflower, turnip, horseradish, broccoli, and Brussels sprouts [22–24] (File 1, Supporting Information). GSL metabolism occurs with two different forms of the enzyme above: plant myrosinase and bacterial myrosinase (from gut microbiota).[21] The plant myrosinase coexists separately with GSLs in plants and becomes active when the plant is affected. While the bacterial myrosinase acts in the colon in the case of denaturation of the plant myrosinase by heat during cooking.[25,26] More than 200 distinct naturally occurring GSLs have been characterized. GSLs are grouped into three main classes depending on the structure of their amino acid precursors: aliphatic, indole, and aromatic GSLs.[23] PEITC is a naturally occurring isothiocyanate in several cruciferous plants.[27] It exists in several cruciferous vegetables as 2-phenylethyl glucosinolate, commonly known as gluconasturtiin (GNST).[28] The distribution of GNST among the members of the family Brassicaceae is summarized in **Table 1**. Like other ITCs, PEITC derives from the hydrolysis of GNST by myrosinase enzyme (**Figure 1**).

The presence of GNST was reported in the seeds of various *Brassica* species [*Nasturtium officinalis* R. Br., (watercress), *Bar-*

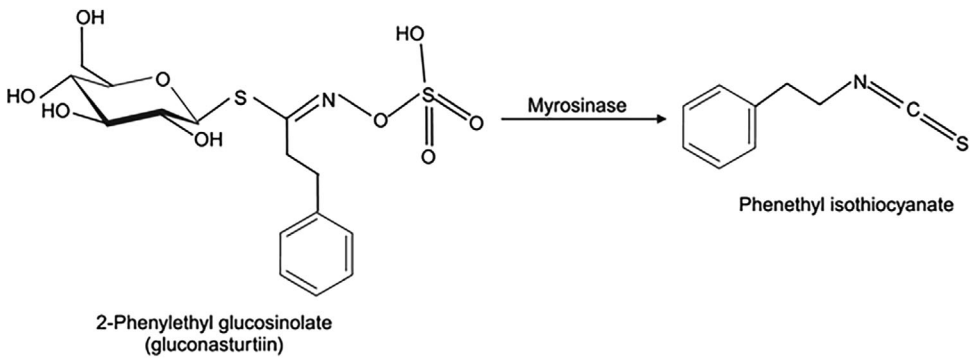

Figure 1. 2-Phenylethyl glucosinolate (gluconasturtiin) hydrolysis by myrosinase enzyme yielding phenylethyl isothiocyanate.

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barea verna (Miller) Asch. (upland cress), *Leavenworthia alabamica* Rollins (Alabama gladecress), *Leavenworthia torulosa* Gray (necklace gladecress), *Rorippa indica* (L.) Hiem (variable leaf yellowcress), *Selenia grandis* R. F. Martin (large selenia), and *Selenia aurea* Nutt. (golden selenia)].[29] *Nasturtium officinale* R. Br., commonly known as watercress, is an aquatic or semi-aquatic plant belonging to the Brassicaceae family. It has creeping or floating angular stems. The leaves are somewhat fleshy, broad-elliptical, alternate, and petiolate with odd-pinnate venation. The plant is native to Europe, North Africa, and Asia and is widely cultivated in many countries. *N. officinale* monograph is presented in German Commission E Monographs[36] and PDR Herbal Medicines.[37] It is a rich GNST source, representing about 80% of its constituents. Several reports detected GNST in different organs of *N. officinale*.[29,31,38,39] In another study, the GNST content in the flower was 9.8, 2.9, 2.2, and 1.3 times more than that in the root, stem, leaf, and seed, respectively.[30] Another biennial edible cruciferous plant that contains GNST is *Barbarea verna* (Mill.) Asch, also known as upland cress.[40] The seeds of *B. verna* were found to have a significant amount of GNST.[33] GNST was reported in several *Brassica* species. *Brassica rapa* subsp. *rapa* L. (turnip) is a cruciferous plant with turnip greens and turnip tops as vegetable crops. Turnip greens are the young leaves, while turnip tops are the fructiferous stems with the flower buds and the leaves surrounding them.[41] PEITC was detected in higher concentrations in the peel (37.38 mmol/100 g Dw) than in peeled roots and leaves of turnip.[42] GNST was determined in the leaves of different varieties of *B. rapa* subsp. *rapa* L. The results showed significant differences in GNST content among the types. However, it represented low content concerning the other detected GSLs.[41] Also, GNST was identified as a minor GSL in turnip greens and turnip tops in different varieties collected from other localities. It represented about 2–3% of their total GSLs content.[43] *B. rapa* spp. *pekinensis* (Chinese cabbage) is widely distributed in Asian countries, mainly China, Japan, and Korea. The changes in total GSLs and PEITC contents in the leaves and midribs upon storage were studied. GSLs were higher in the fresh leaves (148.77 µmol/100 g) than midribs (119.65 µmol/100 g). Upon storage, the GSLs contents increased first and then decreased during further storage. In the fresh samples, PEITC was higher in the leaves (250 µmol/100 g) than in the midribs (150 µmol/100 g). After storage, PEITC was detected in a higher concentration in the midribs than in the leaves.[44] *B. rapa* spp. *pekinensis* (Chinese cabbage) is a rich source of GSLs, especially GNST. The GSL content and composition of 23 genotypes of Chinese cabbage grown in different conditions were analyzed, and GNST was found to be the predominant GSL. GNST was also detected in other Brassica species in considerable amounts in the leaves and roots of *B. rapa* subsp. *chinensis* (pack-choi) and *xBrassicoraphanus* (baemuchae), a generated vegetable formed by hybridization of *Brassica rapa* ssp. *pekinensis* (Chinese cabbage) and *Raphanus sativus* (radish).[45] GNST was detected in five varieties of *B. oleracea* (broccoli, Brussels sprouts, cabbage, cauliflower, and kale),[34] representing a mean relative abundance of 3.1%.[46] GNST was determined in different cultivars of *B. oleracea* var. *capitata* (cabbage), showing a higher root content than the shoots.[47] *B. campestris* L. ssp. *chinensis* var. *communis* (pak-choi) is a valuable *Brassica* crop in East, Northeast, and Southeast Asia. Its roots contained a higher concentration of GNST than its shoots. Also, the variation in GSLs content in the leaf, petiole, and root at different vegetative growth stages during harvest was studied. GNST content increased from day 10 to 20 after transplantation and fell on day 25. Therefore, it was recommended to harvest and consume the plant during the interval from day 20 to 25.[48] *B. rapa* L. (turnip) and *Eruca sativa* L. (arugula) seeds showed the presence of GNST (4.12 and 10.45 µmol g^{-1} DW, respectively).[49] *Raphanus sativus* L (radish) is a biennial plant with thick, fleshy roots. It is native to China and Japan and is cultivated as a vegetable crop worldwide.[50] The predominant GSL in its roots was GNST,[35] which varies among Brassica species.[35] The GSLs content in the seeds, sprouts, shoots, and roots of eight *Brassica* species and *xBrassicoraphanus* (baemuchae) was evaluated. GNST was highest in the roots except in *Raphanus sativus* (radish) (0.12 µmol g^{-1} DW). *B. juncea* (leaf mustard) roots exhibited the highest GNST content (57.76 µmol g^{-1} DW) of all tested samples. Moreover, GNST was the most common GSL detected in all crops studied. It was the dominant GSL in pak-choi shoots. It was not detectable in the *B. oleracea* var. *botrytis* (cauliflower) and radish seeds.[35]

3.2. Chemical Data

ITCs are a class of phytochemicals with remarkable nutritional value and biological activity. These are either aromatic or aliphatic compounds produced in high concentration in plants of family cruciferous, such as cabbage, kale, wasabi roots, broccoli, cauliflower, watercress, sprouts, and Brussel.[51–55] ITCs have the same chemical backbone, R–N = C = S (where R– can be either an aliphatic or aromatic group) **Figure 2**; this radical determines the chemical characteristics of the active compound.[56] Isothiocyanates are reactive electrophiles that covalently modify proteins. The central electrophilic carbon of isothiocyanates (R–N = C = S) undergoes rapid addition reactions with biological nucleophiles, in particular, amines and thiols.[56,57] PEITC is a highly reactive electrophile, prone to nucleophilic attack. Furthermore, PEITC is a compound with low molecular weight (MW = 163.2 g mol).[56,58,59] Chemical characterization of PEITC was performed to identify the characteristics of the structural activity relationship using several spectrophotometric methods (1H-NMR, 13C-NMR, LC-MS/MS, UPLC-DAD/UPLC-ESI-QTOF, IR, and UV spectroscopy) the collected data are shown in Figure 2.[60–62]

3.3. Semi-Synthetic Derivatives

Several naturally occurring derivatives have been identified and reported, while Spencer et al. (2015) succeeded in synthesizing seven PEITC derivatives by four different methods.[63] The authors systematically explored benzyl and phenethyl isothiocyanates' variants to define determinants of inhibition of Macrophage migration inhibitory factor (MIF) tautomerase activity. They introduced hydroxyl, chloro, fluoro, and trifluoro groups at the para and meta positions of the aromatic ring by using four different methods: (Method 1) using thiophosgene in basic conditions (Method 2) hydroxyalkyl and aryl isothiocyanates using carbon disulfide (Method 3) using sodium thiocyanate in acid and (Method 4) using 1,1'-thiocarbonyldiimidazole and base. The obtained derivatives are shown in **Figure 3**.

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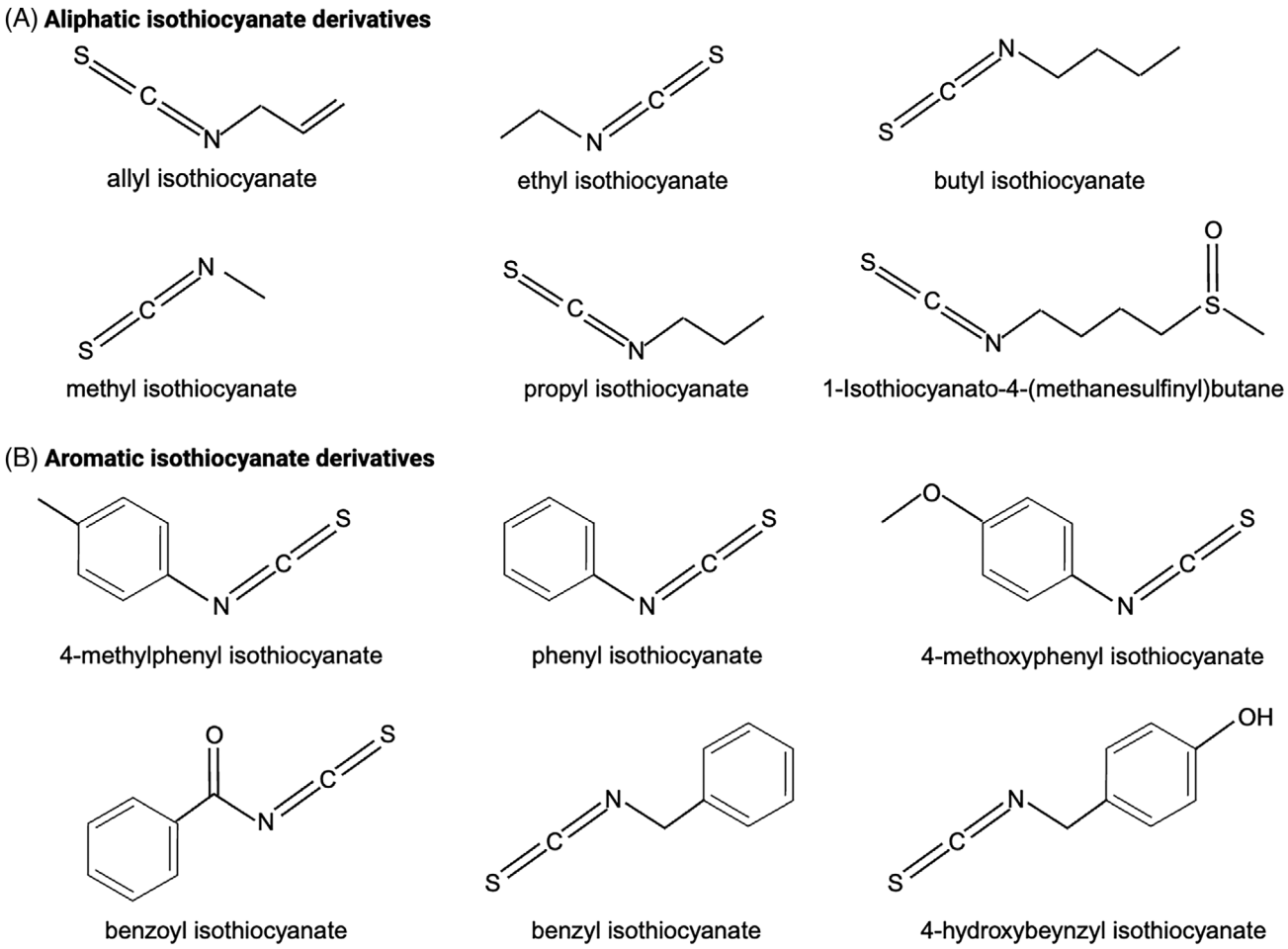

Figure 2. a) Aliphatic isothiocyanate derivatives, b) Aromatic isothiocyanate derivatives.

According to Luo et al., synthesizing PEITC derivatives using acetyl chloride is convenient and effective, yielding products at good to excellent levels.[62] Their study tested the obtained derivatives against two cancer cell lines: Panc 1 (pancreatic cancer) and HGC 27 (gastric cancer). Results showed that para-amide substitution on the benzene ring of PEITC was the most potent modification. Based on this finding, 13 additional derivatives were designed and prepared to further investigate their relationship between structure and activity (**Figure 4**).

3.4. Enzymatic Hydrolysis of Glucosinolates to Isothiocyanates: The Myrosinase-Catalyzed Transformation and Its Implications for Dietary Peitc Bioavailability

An essential aspect of PEITC's bioavailability and biological activity is its formation from glucosinolates, particularly through the process of enzymatic hydrolysis. Glucosinolates (GSLs), present abundantly in cruciferous vegetables, are stable thioester compounds; the transformation into active isothiocyanates, such as PEITC, occurs via the action of the myrosinase enzyme.[64] This enzymatic conversion is typically initiated during the mechanical disruption of plant tissues, notably during the chewing of cruciferous vegetables. The efficiency of this hydrolysis process can vary significantly, influenced by factors such as the plant species, the specific part of the plant being consumed, and the methods of food preparation.[65] For instance, cooking can denature plant myrosinase, leading to reduced hydrolysis efficiency, although bacterial myrosinase in the gut can partly compensate for this loss.[65] The significance of the enzymatic conversion of glucosinolates to isothiocyanates extends beyond the mere chemical transformation; it plays a critical role in determining the dietary intake levels of bioactive compounds like PEITC and, consequently, their potential anticancer benefits.[66] The bioavailability of PEITC, a factor crucial to its anticancer efficacy, is thus closely linked to the dietary habits and food processing methods, underscoring the importance of understanding these processes in the context of nutrition and cancer prevention.[67]

3.5. Impact of Cooking on PEITC Stability

The stability of isothiocyanates, PEITC, during the cooking of cruciferous vegetables is a critical factor influencing their health benefits and cooking cruciferous vegetables, a common dietary source of PEITC, can significantly affect the compound's

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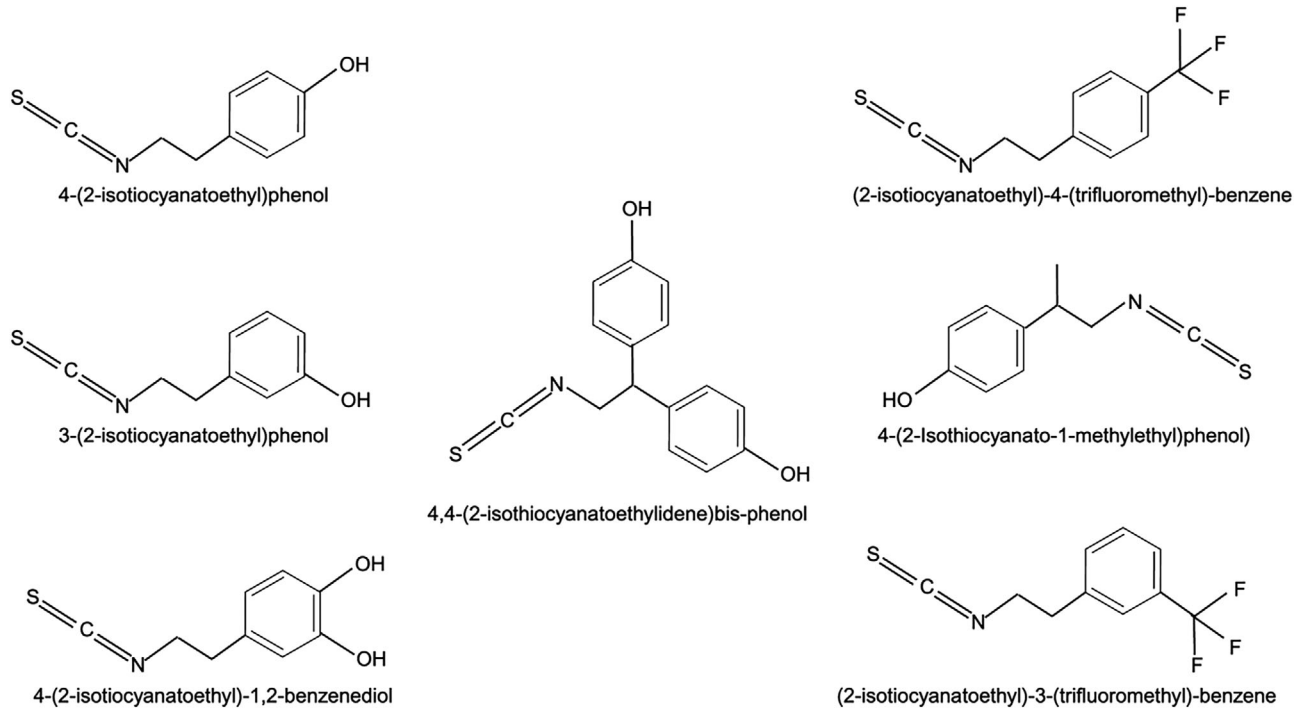

Figure 3. Phenethyl isothiocyanate (PEITC) derivatives were obtained with hydroxyl, chloro, fluoro, and trifluoro moieties at the para and meta positions.

beneficial health properties.[68,69] Isothiocyanates, including PEITC, are thermally labile, meaning they are susceptible to decomposition under heat; during cooking, these compounds undergo thermal degradation, resulting in a reduction of their concentration in the food.[70] A major pathway of this thermal decomposition involves the formation of derivatives of thiourea. These derivatives, while not necessarily harmful, do not possess the same bioactive properties as the intact isothiocyanates. The degradation into thiourea derivatives, therefore, potentially diminishes the anticancer efficacy attributed to these compounds when consumed in their natural, uncooked form.[69] This thermal sensitivity underscores the importance of considering cooking methods when evaluating the dietary intake of PEITC and its associated health benefits. It highlights a critical aspect of food science and nutrition, where the preparation method can directly influence the bioavailability and efficacy of bioactive compounds.[71] Understanding this thermal decomposition process is essential for both dietary recommendations and the development of effective cancer prevention strategies involving PEITC.

4. Pharmacokinetics of PEITC

The pharmacokinetic profile of PEITC, including its absorption, distribution, metabolism, and excretion, remains largely unclear. Previous studies have reported that PEITC is rapidly absorbed in the gastrointestinal tract after oral ingestion and reaches peak plasma levels within 0.5–1 h in rodents.[72] PEITC distributes widely in the body and can penetrate biological barriers, as evidenced by its detection in various organs such as the liver, lung, and prostate after oral administration.[72,73] The main metabolic pathway of PEITC involves conjugation with glutathione, a tripeptide that facilitates xenobiotic detoxification. Subsequently, the glutathione conjugate is metabolized via the mercapturic acid pathway, resulting in *N*-acetylcysteine conjugates.[73] The urinary excretion of PEITC and its metabolites accounts for most of the elimination route.[73] A recent preclinical pharmacological study investigated the dose-dependent pharmacokinetics and oral bioavailability of PEITC in Sprague–Dawley rats. The findings showed that PEITC was stable in biological samples, especially under refrigerated conditions. It had significant binding to serum proteins, with a free fraction of 0.019 in rat serum. Pharmacokinetic analysis revealed that at a low dose of 2 μmol kg^{-1}, the clearance was 0.70 ± 0.17 L h^{-1} kg^{-1}, and the apparent volume of distribution was 1.94 ± 0.42 L kg^{-1}. At higher doses, the clearance decreased while the apparent volume of distribution increased, indicating non-linear elimination and distribution processes. PEITC exhibited high oral bioavailability, with values of 115% and 93% at 10 and 100 μmol kg^{-1} doses, respectively.[74] A clinical trial found that most of the orally administered PEITC was excreted in urine within 24 h.[75]

Only a few studies provided some understanding of the pharmacokinetics of PEITC; more research, particularly in humans, is needed to fully understand this compound's absorption, distribution, metabolism, and excretion.

5. Mechanisms of Antitumor Action of Phenethyl Isothiocyanate

Targeting the different hallmarks of cancer can be a good choice for developing new preventive and therapeutic strategies.[76,77] PEITC has been proven to control and treat cancer by modulating the survival and signaling pathways, inducing apoptosis,

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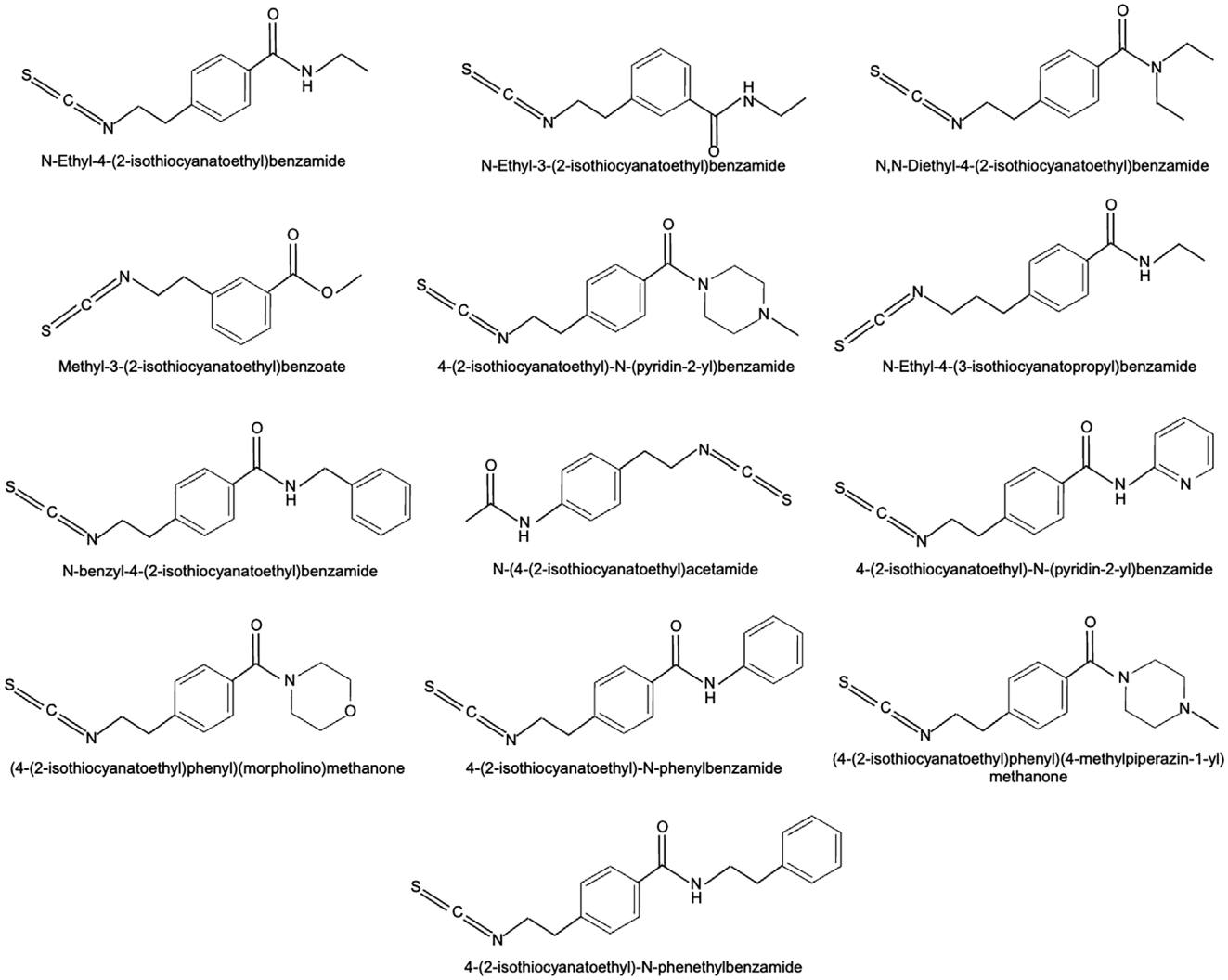

Figure 4. Acetyl chloride-mediated synthesis of phenethyl isothiocyanate (PEITC) derivatives.

arresting the cell cycle, and modulating the effect of drug-metabolizing enzymes (**Figure 5**).

5.1. Apoptosis Induction

Apoptosis is a form of planned cell death to defend against cancer incidence and maintain tissue homeostasis.[78,79] For instance, three main pathways can initiate apoptosis: the intrinsic pathway that is mediated by the mitochondria,[80] the extrinsic pathway that is mediated by the death receptors on the cell surface,[80] and the endoplasmic reticulum stress pathway that is mediated by the imbalance in the levels of different elements in the endoplasmic reticulum.[79,81]

5.1.1. The Intrinsic Pathway

The mitochondria are a vital cell component for producing energy in healthy cells and the transduction of apoptotic pathways in cancer cells.[82] Several studies proved that PEITC could initiate oxidative damage in the mitochondria by increasing the intracellular ROS to a highly toxic level through binding to c-glutamate-cysteine-glycine (GSH) (with the aid of the conjugating enzyme S-transferase (GST)) and reducing its activity as an antioxidant enzyme.[81] The accumulation of PEITC-induced ROS can cause lipid peroxidation of the mitochondrial membrane and, therefore, the loss of membrane integrity and the production of apoptosis-inducing factor (AIF) and apoptogenic cytochrome c (Cyt c).[83] PEITC can also increase the cytosolic levels of various cytokines, activating the caspase enzymes in the apoptotic pathway and can induce the opening of the permeability transition pore (PTP), an unselective voltage-dependent mitochondrial channel.[84] The opening of the PTP disrupts the transmembrane potential, causes matrix swelling, releases Cyt c, and triggers cell apoptosis.[84]

Additionally, PEITC can regulate the intracellular expression of proapoptotic proteins (Bax and Bid) and antiapoptotic proteins (Bcl-2, Bcl-xL, X-linked inhibitor of apoptosis protein (XIAP), and

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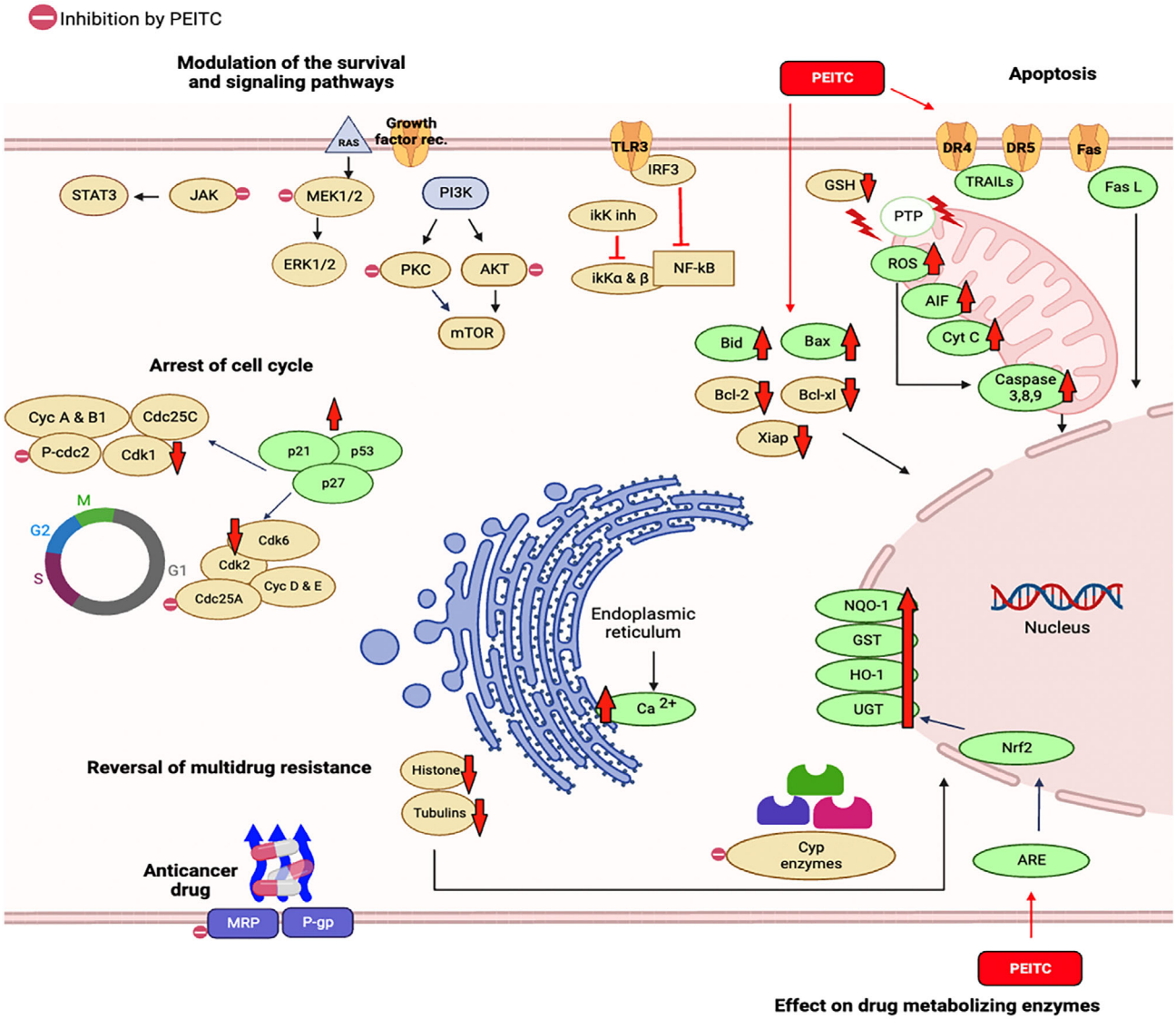

Figure 5. Different mechanisms underlying the efficacy of PEITC as an anticancer agent, AIF: Apoptosis inducing factor, ARE: Adenine/uridine-rich element, Bax: B-cell leukemia/lymphoma 2-associated X protein, Bcl-2: B cell lymphoma-2, Bcl-Xl: B-cell lymphoma-extra large, Bid: BH3 interacting-domain, Ca^{2+}: Calcium ion, CDC25A: Cell division cycle 25 homolog A, Cdc25C: Cell division cycle 25 homolog C, Cdk1: Cyclin-dependent kinase 1, Cdk 2: Cyclin-dependent kinase 2, Cdk 6: Cyclin-dependent kinase 6, Cyc A: Cyclin A, Cyc B1: Cyclin B1, Cyc D: Cyclin D, Cyc E: Cyclin E, Cyp: Cytochromes, Cyt c: Cytochrome C, DR4: Death receptors 4, DR5: Death receptors 5, ERK: Extracellular signal-regulated kinase, Fas: Fibroblast-associated, Fas L: Fibroblast-associated ligand, GSH: c-glutamate-cysteine-glycine, GST: Glutathione transferases, HO-1: heme oxygenase1, Ikk inh: I-κB kinase, ikkα and β: I-κB kinase α and β, JAK: Janus kinase, MEK1/2: MAPK/ERK kinase 1/2, MRP: Multidrug resistance proteins, mTOR: Mammalian target of rapamycin, NF-κB: Nuclear factor-kappa B, NQO1: NAD(P)H quinone oxidoreductase 1, Nrf: Nuclear respiratory factor, P-cdc2: Phosphorylated-cell division cycle 2, PEITC: Phenethyl isothiocyanate, P-gp: P-glycoprotein, PI3K: Phosphoinositide 3-kinases, PKC: Protein kinase C, PTP: Permeability transition pore, Hsp27: Heat shock protein 27, HSP90: Heat shock protein 90, RAS: Rat sarcoma virus, ROS: Reactive oxygen species, STAT 3: Signal transducer and activator of transcription 3, TLR 3: Toll-like receptor 3, TRAILs: Tumor necrosis factor (TNF)-related apoptosis-inducing ligand, UGT: UDP-Glucuronosyltransferases, Xiap: X-linked inhibitor of apoptosis protein.

survivin), leading to reduced membrane integrity, Cyt c release, and caspase-dependent cell apoptosis.[85]

5.1.2. The Extrinsic Pathway

The death receptors such as death receptors 4(DR4) and death receptors 5 (DR5) are transmembrane proteins, where Tumor necrosis factor-related apoptosis-inducing ligands (TRAILs) can bind to them and initiate cell apoptosis.[86] Studies have demonstrated that PEITC can enhance TRAIL-induced apoptosis by upregulating DR4 and DR5 expression.[87] Fibroblast-associated (Fas) is another death receptor that mediates apoptotic signals when bound to Fas ligands. This complex activates the caspase enzyme family and triggers cell apoptosis.[81]

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5.1.3. The Endoplasmic Reticulum Stress Pathway

Cell apoptosis can result from disrupting some critical components within the cell. PEITC has been reported to induce the transfer of calcium ions (Ca^{2+}) from the endoplasmic reticulum to the mitochondria by stimulating the phospholipase C-dependent Ca^{2+} release and Ca^{2+} entry channels, which can activate various apoptotic pathways.[88] Moreover, PEITC has an electrophilic property that enables it to covalently bind to nucleophilic groups such as RNA, deoxyribonucleic acid (DNA), and amino acids.[89] PEITC has been shown to interact with different proteins in cancer cells, thereby causing epigenetic changes that alter their functions.[89] For example, PEITC has been demonstrated to bind to glutathione, Cyps, α- or β-tubulin, histone, heat shock proteins (HSPs), GRP78, ADAM, topoisomerase IIα, caspase-like, and trypsin-like enzymes, which are all essential for cell survival and normal cell cycle.[90,91]

5.2. Antiproliferative: Cell Cycle Arrest Induction

Cell progression and proliferation involve the sequential transition of these phases: G0, G1, S, G2, and M.[92] Suppressing the proliferation of cancer cells depends on targeting different cyclin-related proteins, cyclin-dependent kinases (CDK), and their inhibitors.[92,93]

5.2.1. G0/G1 Phase

PEITC has been reported to induce G0/G1 phase arrest by decreasing the expression of CDK6, cell division cycle 25 homolog A (CDC25A), CDK2, phospho-Rb, cyclin D, and cyclin E proteins, as well as increasing the expression of cyclin-dependent kinase inhibitors p15, p27, p53, and p21.[94] Furthermore, several studies have verified that PEITC could downregulate the expression of the BAG3 family, an essential mediator in surviving the tumor cell, a key mediator in tumor cell survival, through G0/G1 phase arrest.[95,96]

5.2.2. G2/M Phase

PEITC can arrest the cell cycle at phase G2/M cell by suppressing the expression of cyclin A and B1, Cdk1, Cdc25C, and phosphorylated-cell division cycle 2 (p-cdc2), as well as increasing the expression of p21, p27, p53, and 14-3-3ϵ through the ataxia telangiectasia mutated/ataxia telangiectasia and Rad3-related (ATM/ATR) pathway,[97–100] an essential pathway in controlling genome integrity and cell cycle.[101,102] A more interesting finding was that PEITC-*N*-acetylcysteine (NAC), a metabolic product for PEITC, showed the same activity as an antitumor agent through downregulating the expression of Cdk1 and cyclin B1.[103–106]

5.3. Modulation of the Survival and Signaling Pathways

Cell survival, proliferation, differentiation, and angiogenesis are regulated by a series of pathways that include the Nuclear factor kappa B (NF-κB) survival pathway, the Akt (protein kinase B) survival pathway, the Janus kinase (JAK)-STAT signaling pathway, and p38 mitogen-activated protein kinase (MAPK) survival pathway.[107,86]

5.3.1. The Nuclear Factor Kappa B (NF-κB) Survival Pathway

The NF-κB pathway is crucial in cancer cell growth, proliferation, and survival. NF-κB is normally sequestered in the cytoplasm by IκKα/β proteins; when external stimuli (cancer case) activate IκK inhibitors, they phosphorylate and degrade IκK proteins, releasing and translocating NF-κB to the nucleus for cell survival.[108,109] PEITC exhibits anti-inflammatory activity by suppressing NF-κB activity.[110] This activity may result from the direct inhibition of IκK or the toll-like receptor 3 (TLR3)-mediated Interferon regulatory factor (IRF3) signaling pathway (another regulator of NF-κB activation).[111]

5.3.2. The JAK-STAT Signaling Pathway

The JAK-STAT signaling pathway is an essential mediator in the metastasis of cancer cells. PEITC can hinder the activation of the JAK-STAT3 pathway,[112] decreasing the expression of MMP2 and MMP9. Matrix metalloproteinase (MMP) is an enzyme that destroys the extracellular matrix's collagen and is critical in cell metastasis.[113]

5.3.3. The MAPK Survival Pathway

The invasion and metastasis of cancer cells are mediated by MAPK pathways such as P38 and ERK1/2.[114] Scientific evidence proved PEITC can inhibit Akt and ERK1/2 pathways.[115] Furthermore, it can inhibit mitogen-activated protein kinase kinase 7 (MKK7) and MAP kinase3 (MEKK3).[110] Several studies also proved the efficacy of PEITC in inhibiting the protein kinase C (PKC)/MAPK pathway.[116,117] Additionally, PEITC can reduce the expression of HIF-1α by inhibiting the MAPK pathway.[118,119]

5.3.4. The Akt Survival Pathway

Abnormal proliferation is a central hallmark of cancer cells. The phosphatidylinositol 3 kinase (PI3K)/Akt pathway, essential for cell proliferation, can be activated by Ras proteins. PEITC can inhibit this pathway, reducing cancer cell proliferation without directly targeting Ras protein.[120,121] Akt1, Akt2, and Akt3 (protein kinase B or PKB$\alpha/\beta/\gamma$, respectively) are activated by recruitment to the cell membrane via PI3K.[122] PEITC can also inhibit human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR), the primary growth factor receptors and regulators of Akt.[123] Moreover, PEITC can inhibit angiogenesis in cancer cells by suppressing the expression of HIF-1α (an essential factor released in cancer cells under hypoxia status to secrete VEGF) and VEGF (a promotor of angiogenesis) through the PI3K/Akt pathway. Further, PEITC proved to affect the Akt/JNK/Myeloid cell leukemia-1 (Mcl-1) pathway by inhibiting the Akt pathway, activating Jun *N*-terminal kinase (JNK), and downregulating the Mcl-1.[120] Additionally, PEITC can suppress the Akt/mammalian target of rapamycin (mTOR) signaling pathway to initiate autophagy of cancer cells.[124]

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5.3.5. Targeting COX-2, an Oncogenic Protein: Molecular Interactions and Structure-Activity Relationship of PEITC

COX-2 is an inducible enzyme that plays a crucial role in the inflammatory response and has been identified as a promoter of oncogenic processes.[125] Its overexpression is frequently observed in various cancers and is linked to enhanced tumor growth, angiogenesis, immune evasion, and metastasis and this makes COX-2 a strategic target for anticancer therapies.[125] PEITC has a molecular structure, characterized by an electrophilic isothiocyanate group which is pivotal for its biological activity; this group enables PEITC to interact covalently with nucleophilic sites on target proteins, including COX-2.[126]

The interaction of PEITC with COX-2 encompasses more than mere enzymatic inhibition. PEITC modulates COX-2 expression at the transcriptional level, predominantly through the downregulation of NF-κB, a transcription factor that regulates COX-2 expression. This results in attenuated prostaglandin synthesis, a key factor in tumorigenesis.[127] Additionally, PEITC's influence extends to various signaling pathways intertwined with COX-2 activity, notably the PI3K/Akt pathway, linking its COX-2 modulatory effects to broader anticancer activities.[6, 128] The unique molecular structure of PEITC allows it to induce oxidative stress and modulate key proteins involved in cell cycle regulation and apoptosis, pathways in which COX-2 plays a contributory role.[6] This multifaceted interaction highlights the potential of PEITC not only as a direct inhibitor of COX-2 but also as a modulator of the complex network of oncogenic pathways associated with COX-2 upregulation.

5.4. Effect on Drug Metabolizing Enzymes

Drug metabolizing enzymes play a central role in the metabolism and elimination of drugs, protecting our bodies from the possible carcinogenic process of various medications. PEITC can prevent these harmful insults by inhibiting phase I enzymes and activating phase II enzymes.

5.4.1. Inhibition of Phase I Enzymes

PEITC proved to inhibit the activity of some CYP enzymes through binding to their amino acid residues.[129] PEITC can attach to the *N*-terminal residues of lysine or proline and the OH group from tyrosine residues.[130]

5.4.2. Activation of Phase II Enzymes

PEITC can activate various phase II enzymes such as GST, quinonereductase (QR), NAD(P)H quinone oxidoreductase1 (NQO-1), UDP-glucuronosyltransferases (UGT), and heme oxygenase1 (HO-1) that are responsible for the conjugation detoxifying reactions.[131–133] PEITC also activates adenine/uridine-rich element (ARE), a central mediator in phase II metabolism through JNK1 and Nrf2 pathways.[134]

5.5. Reversal of Multidrug Resistance

Multidrug resistance to chemotherapy is considered a critical problem nowadays. PEITC can increase the accumulation of antitumor drugs by inhibiting P-gp/ multidrug resistance 1 (MDR1), multidrug resistance-associated protein 1 (MRP1), and MRP2, the key uptake and efflux transporters for these drugs.[135–137]

Table 2 provides an overview of the antitumor mechanisms of PEITC, targeting different hallmarks of cancer.

6. Exploring the Anticancer Properties of PEITC: Mechanistic Approaches

In vivo and in vitro studies have tested the efficacy of PEITC in preventing and treating cancer.[28, 139–141] In this section, we first review the results of the in vitro studies on PEITC, and then we mention some studies that used animal models to assess the antitumor effects of PEITC.

The antitumor studies of PEITC have been performed in breast, lung, colon, leukemia, glioblastoma, cholangiocarcinoma (chemo-resistant cancer with poor prognosis cancer), squamous cell carcinoma, and pancreatic cancer cell lines.[142–145] The action mechanisms follow different pathways (see Section 5). However, some key molecules have been identified as involved in the sensitivity to PEITC-induced apoptosis. For example, PEITC regulates the expression of NRF2 transcription factor in breast cancer cells, a key to provoking apoptosis.[146] Also, PEITC is an inhibitor of heat shock proteins (related to regulating transcription, transduction, and cell cycle control) expressed in many cancers.[147] In pharmacological studies, the induction of ROS in cancer cells by PEITC is important for triggering cell death. Tusskorn et al. suggested that PEITC enhances oxidative stress in cholangiocarcinoma due to antioxidant enzyme depletion, induction of superoxide formation, and loss of mitochondrial transmembrane potential.[142] Similarly, Gupta and Srivastava found that treating M.D.+Anderson+–+Metastatic+Breast+231 (MDA-MB-231) cells with 10 µM of PEITC caused ROS generation and mitochondrial depolarization, leading to the release of Cyt c and apoptosis mediated by activation of caspase-3, indicating that the mitochondrial membrane potential is compromised by ROS generation.[148] The activation of caspase-3 by PEITC was also documented in an article that evaluated the apoptotic effects of this compound in human cervical cancer cells.[138]

Also, in vitro studies demonstrated that PEITC inhibited the protein and gene expression of interleukins 6, 1β, and TNF-α in human glioblastoma cells. Thus, PEITC could act as an anti-inflammatory agent in cancer cells.[149]

Diverse cancer cell lines have been used as a model to test PEITC's effectiveness in in vivo studies. Hahm and Singh utilized the BRI-JM04 cell line derived from a mammary tumor of a transgenic mouse, observing inhibition of cell viability and an increase of apoptosis. They aimed to evaluate the proapoptotic response to PEITC and its ability to counteract mammary cancer. Their study offered a platform to explore the cellular mechanisms directly in vivo.[150]

Regarding the studies with animal models, Stan et al. demonstrated that oral administration of PEITC reduced pancreatic cancer cell growth in a MIAPaca2 xenograft animal model of 6 weeks old.[144] PEITC also can participate in cancer prevention. Aras et al. documented that administering 50 or 150 µmol kg^{-1} chronically of PEITC to Sprague–Dawley rats with breast cancer re-

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Table 2. Potential mechanistic pathways targeted by PEITC in cancer.

Effects on hallmark cancer	Mechanisms	Key pathways/targets	References
Apoptosis induction	↑ programmed cell death	Intrinsic, extrinsic, ER stress pathways	[78, 79]
Intrinsic pathway	targets mitochondria to induce oxidative damage	ROS, GSH, Cyt C	[81]
Extrinsic pathway	↑TRAIL-induced apoptosis by upregulating death receptors	DR4, DR5, Fas	[86, 138]
ER stress pathway	↑ Ca^{2+} transfer from ER to mitochondria	Phospholipase C-dependent Ca2+ release	[88]
Antiproliferative: cell cycle arrest	↓cancer cell proliferation	G0/G1, G2/M phases	[92]
G0/G1 phase	↑G0/G1 phase arrest by modulating expression of CDK and cyclins	CDK6, CDC25A, CDK2, cyclin D, cyclin E	[94, 95, 96]
G2/M phase	↑cell cycle at G2/M phase	Cyclin A, B1, Cdk1, Cdc25C	[97, 98, 99, 100]
Modulation of survival and signaling	Affects several pathways that regulate cell survival, proliferation, and differentiation	NF-κB, Akt, JAK-STAT, MAPK	[86, 107]
NF-κB Pathway	↓NF-κB	IκK, TLR3-mediated IRF3 signaling	[110, 111]
JAK-STAT pathway	hinders activation of JAK-STAT3 pathway	MMP2, MMP9	[112, 113]
MAPK pathway	↓Akt, ↓ERK1/2	P38, ERK1/2	[115, 116, 117]
Akt pathway	↓PI3K/Akt pathway and its downstream targets	Akt1, Akt2, Akt3, HER2, EGFR	[120, 121]
Effect on drug-metabolizing enzymes	alters the activity of phase I and phase II enzymes	CYP enzymes, GST, QR, NQO-1	[129]
Phase I inhibition	↓CYP enzymes	Lysine, proline, tyrosine residues	[130]
Phase II activation	activates various phase II enzymes	GST, QR, NQO-1, UGT, HO-1	[131, 132, 133]
Reversal of multidrug resistance	↑accumulation of antitumor drugs by inhibiting transporters	P-gp/MDR1, MRP1, MRP2	[135, 136, 137]

Abbreviations: Akt: Protein kinase B; ARE: Antioxidant response element; ATM/ATR: Ataxia telangiectasia mutated/ATM and Rad3-related; BAG3: Bcl-2-associated athanogene 3; Cao: Calcium oxide; Cdc: Cell division cycle; CDK: Cyclin-dependent kinase; Cdk: Cyclin-dependent kinase; Cyt c: Cytochrome C; DR4, DR5: Death receptor 4, death receptor 5; EGFR: Epidermal growth factor receptor; ER: Endoplasmic reticulum; ERK: Extracellular signal-regulated kinases; GSH: Glutathione; GST: Glutathione S-transferase; HER2: Human epidermal growth factor receptor 2; HIF-1α: Hypoxia-inducible factor 1-alpha; HO-1: Heme oxygenase 1; IκK: Inhibitor of nuclear factor kappa B kinase; IRF3: Interferon regulatory factor 3; JAK-STAT: Janus kinase-signal transducer and activator of transcription; JNK: Jun *N*-terminal kinase; MAPK: Mitogen-activated protein kinase; MEKK3: Mitogen-activated protein kinase kinase kinase 3; MRP: Multidrug resistance-associated protein; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa B; NQO-1: NAD(P)H quinone dehydrogenase 1; Nrf2: Nuclear factor erythroid 2-related factor 2; P-gp: P-glycoprotein; PEITC: Phenethyl isothiocyanate; PI3K: Hosphatidylinositol 3-kinase; PKC: Protein kinase C; PTP: Permeability transition pore; QR: Quinone reductase; ROS: Reactive oxygen species; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; UGT: UDP-glucuronosyltransferase; VEGF: Vascular endothelial growth factor. Symbols: ↑increased, ↓decreased.

duced the incidence of mammary tumors, decreased invasive tumors, and reduced angiogenesis in the treated groups.[151]

Combining PEITC with known chemotherapeutic agents can combat clinical chemoresistance and provide a new approach to clinical therapy.[152] The impact of PEITC in combination with other phytochemicals such as resveratrol, indole-3-carbinol, xanthohumol,[153,154] and curcumin[155] in antitumoral treatment has been tested in vitro cancer models and in vivo.[152] A study made with transformed human liver epithelial-2 (THLE-2) and Hepatoma+G2 (HepG2) cells exposed to xanthohumol plus PEITC has observed induction of apoptosis in contrast to exposure to single compounds. Hence, the authors suggested that this combination may be helpful in hepatocellular carcinoma therapy.[153] Similar results were reported by Krajka-Kuźniak et al., who demonstrated that exposure of pancreatic cancer cells to xanthohumol plus PEITC leads to a reduction of its proliferation.[154]

In summary, the anticancer effect exhibited by PEITC has been favorable at different doses, as shown in **Table 3**. A challenge to consider is its evaluation of pathways related to the effects produced as an adjuvant of chemotherapeutic drugs and the pathways and effective dose involved with the synergic effect reported in many studies.

7. Strategies to Increase PEITC Therapeutic Efficacy in Cancer Therapy

7.1. Nano-Formulations for Improving Bioavailability of PEITC

PEITC is a potential anticancer agent that can modulate multiple signaling pathways related to tumor initiation, growth, and metastasis. Nonetheless, its low bioavailability impedes its clinical application as an oncologic treatment.[72] Several factors influence the bioavailability of PEITC, including its physicochemical properties, metabolism, and route of administration. PEITC is a lipophilic compound with poor water solubility, which hinders its dissolution and absorption in the gastrointestinal tract.[72] Furthermore, rapid metabolism and elimination limit the systemic exposure of PEITC, reducing its efficacy against cancer cells.[73]

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Table 3. Pharmacological experimental studies on the anticancer effect of PEITC with their possible mechanisms of action.

Type of study in vitro/in vivo	Concentration/dose	Type of cancer/experimental model	Mechanisms/effects	Ref.
In vitro	IC_{50} = 20 μM	Breast cancer/MCF7, ZR-75-1, BT549, MDA-MB-231, T47D, SKBR3 cell lines	↑apoptosis ↓Bcl-2, ↑Bax, ↓GSH, ↑caspases 3, 9 ↑cell cycle arrest, ↑G2/M phase	[146]
	IC_{50} = 4, 8, 12 μM	Glioblastoma/GBM 8401 cell line	↓Akt, ↓ERK, ↓NF-κB ↓proinflammatory cytokines through the ↓PI3K/Akt/NF-κB pathway.	[149]
	Xanthohumol and PEITC: 5, 10, and 20 μM	Hepatocellular carcinoma/ THLE-2 and HepG2 cell lines	↑ cytotoxicity in combination with Xanthohumol ↑SOD, ↑NQO-1, ↑Nrf2/ARE, ↓NF-κB	[153]
	IC_{50} = 0.1, 0.5, 2.5, 5 μM	Breast cancer/MCF7 and MDA-MB-231cell lines	Epigenetic modification of HSP90. ↑G2/M cell cycle, ↓Cyclin B1, ↓CDK1, ↓Cdc25C, ↑caspase-dependent apoptotic pathway.	[147]
	IC_{50} = 2.5, 5 μM	Breast, colon cancer MCF-7, HCT-116, and HCT-116 cell lines	↑apoptosis ↓Bcl-2, ↓Bcl-xl	[150]
	IC_{50} = 0–20 μM	Breast cancer/MCF-7, PTEN-deficient MEF, and TSC2-deficient MEF cell lines	↓cell proliferation ↓metastasis, ↓Akt, ↓ERK ↑autophagy through suppressing the mTORC1	[124]
	IC_{50} = 3 μM/10 or 30 μM of PEITC	Breast cancer/MCF-7 cell line	Epigenetic reduction of Hsp27 ↑p57, ↑p53	[156]
	IC_{50} = 5, 10, 15 μM/4, 10 μM of PEITC	Breast cancer/MCF-7, MCF-7 high in HER2, MDA-MB-231, and MDA-MB-231 high in HER2 cell lines	↓ cell proliferation, ↓HER2, ↓EGFR, ↓Akt ↓metastasis, ↓STAT3 ↑apoptosis, ↑Bax, ↓Bcl-xl, XIAP	[148]
	IC_{50} = 5, 10 μM/2.5, 5, 10 μM	Cervical cancer/HEP-2 and KB cell lines	↑apoptosis, ↑DR4, ↑ DR5 receptors, ↑Cyt C, ↑ Bax, ↑Bid, ↓Bcl-2, ↓Bcl-xl, ↓ERK, ↓MEK	[138]
	IC_{50} = 3, 3.5/1, 3, 10 μM	Cholangiocarcinoma/KKU-M214 cell line	↑apoptosis, ↑free, calcium level in the cytosol, ↑production of Cyt C, ↑AIF, ↑Bax	[157]
	IC_{50} = 6.6, 3.8/3–10 μM	Cholangiocarcinoma/KKU-100 cell line	↑apoptosis, ↑Cyt C, ↑AIF, ↑ caspases 3, 8, 9	[142]
	25–50 μM	cDNA of CYP2E1 from *E. coli* MV1304	inactivation of CYP2E1	[158]
	2.5, 5, 10 μM	Myeloid leukemia/HL-60, human topoisomerase IIα	↓topoisomerase IIα through its thiol modification ↑ apoptosis	[143]
	IC_{50} = 7.7 μmol/L/2.5, 5, 10 μmol L^{-1}	Pancreatic cells/MIAPaca2, PL-45, and BxPC3 cell lines	↓ tumor growth in a dose-dependent way, ↑G2/M phase cell cycle arrest; ↓Bcl-2, ↓Bcl-XL, ↑Bak, ↓Notch 1 and 2. Cleavage of poly-(ADP-ribose) polymerase and so increased histone-associated DNA fragmentation.	[144]
	Xanthohumol and PEITC: 1–150 μM	Pancreatic cancer/PANC-1 cell line	Xanthohumol and PEITC combination showed a reduction in the binding of NF-κB/p65 subunits to DNA as well as an increase in the activation of Nrf2 followed by an increase in the expression of NQO1 and SOD.	[154]
	0.5% *v/w* PEITC topical gel	Squamous cell carcinoma/squamous cancer cell line on a Strat-M skin-like membrane	↓cell viability with perfect viscosity and transdermal diffusion tests.	[145]
	12 μmol/day orally, 5 days/week for 7 weeks	Pancreatic cancer/MIAPaca2 xenograft mouse model	↓tumor growth ↑apoptosis, ↑G2/M phase cell cycle arrest	[144]
	50 and 150 μmol kg^{-1} orally Every 2 days for 18 weeks before tumor induction	Breast cancer/NMU-induced breast cancer in Sprague Dawley rats	Chemopreventive effect ↑normal cell survival from tumor incidence	[151]
	25 mg kg^{-1} twice/day orally, once a week for 3 weeks	Lung cancer/A2780 and A549/CDDP xenografts in nude BALB/c mice	↓ cancer cell survival through depletion of GSH	[159]

(*Continued*)

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Table 3. (Continued)

Type of study in vitro/in vivo	Concentration/dose	Type of cancer/experimental model	Mechanisms/effects	Ref.
	3 μmol g^{-1} diet for 29 weeks	Breast cancer/MMTV-neu mice	Chemopreventive effect through inhibiting angiogenesis and tumor growth	[141]
In vivo	Curcumin (3 and 6 μmol kg^{-1}) with PEITC (2.5 and 5 μmol kg^{-1}) thrice/week for 28 days, before tumor implantation	Prostate cancer/PC-3 xenografts immunodeficient mouse model	Combination of curcumin with PEITC significantly suppressed the growth and proliferation of PC-3 xenografts through inhibiting the Akt and NF-κB pathways.	[155]
	50 mg/kg, i.p. for 20 days after the transplantation of U937 human leukemia cells	Leukemia/U937 xenograft NOD/SCID mouse model	↓ tumor growth and induction of apoptosis through deactivating the Akt, ↑JNK pathways, ↓Mcl-1	[120]

Abbreviations and symbols: ↑increase, ↓decrease, AIF: Apoptosis inducing factor, Akt: Protein kinase B, Bax: Bcl-2-associated X protein, bcl-2: B cell lymphoma-2, Bcl-Xl: B-cell lymphoma-extra large, CDC25C: Cell division cycle 25 homolog C, CDK 1: Cyclin-dependent kinase 1, Cyt c: Cytochrome c, DNA: Deoxyribonucleic acid, DR4: Death receptors 4, DR5: Death receptors 5, EGFR: Epidermal growth factor receptor, ERK: Extracellular signal-regulated kinase, GSH: c-glutamate-cysteine-glycine, HeLa: Henrietta Lacks cell line, Hep-2: Human epithelial cell line 2, HepG2: Hepatoma+G2, HER2: Human epidermal growth factor receptor 2, i.g.: Intragastrically, IC_{50}: Half maximal inhibitory concentration, IP: Intraperitoneal, MAPK: Mitogen-activated protein kinases, MCF-7: Michigan cancer foundation-7, Mcl-1: Myeloid cell leukemia-1, MDA-MB-231: M.D.+Anderson+−+Metastatic+Breast+231, MEK: Mitogen-activated protein kinase, mTORC1: Mechanistic target of rapamycin complex 1. NF-κB: Nuclear factor-kappa B, NMU-induced: Neuromedin U-induced, NOD/SCID: Nonobese diabetic/severe combined immunodeficiency, NQO1: NAD(P)H quinone oxidoreductase 1, NSCLC: Non-small cell lung cancer, PEITC: Phenethyl isothiocyanate, PERK/2α-CHOP/Noxa: Protein kinase RNA-like ER kinase/2α-C/EBP homologous protein/Noxious agent, PI3K: Phosphoinositide 3-kinases, SOD: Superoxide dismutase, THLE-2: Transformed human liver epithelial-2, TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand, μM: Micromolar.

Otherwise, the pharmacokinetic aspects of release, absorption, and distribution are diminished, resulting in poor pharmacological efficacy or high variations in the effect during in vivo systems monitoring. Even on some occasions, it is notable to observe pharmacological administration methods that include organic solvents that are not permissible for animal models because the drug is very lipophilic. Although there are some reports on the fabrication and evaluation of nanosystems with PEITC, the evidence is still limited. As can be seen in **Table 4**, different types of nanoparticles encapsulate PEITC, the best known include metallic nanoparticles, protein, liposome, solid lipid nanoparticles, polymer conjugate, nanoemulsion, and quantum dots. Interestingly, examples of the purely polymeric type of nanoparticles have not been included so far. In Table 4, each type of nanosystem represents qualities and certain limitations that will depend on the pharmacological application; cost-effective analysis is necessary to make an appropriate decision. Remarkably, most reports mention high percentages of encapsulation efficiency of PEITC in nanosystems, which is promising for all biological applications. Likewise, nanometric size values less than 200 nm are reported. However, it also highlights that PEITC can be dual-loaded as an adjuvant molecule for some pharmacological models; this means that studies show that the interest in PEITC predominates as an adjuvant and not as the main drug. This is why some of the studies included in Table 4 describe the application of PEITC in solution independent of the nanoformulation with another drug loaded, and in other studies PEITC plus a chemotherapeutic agent. The predominant lack of information in studies of nanosystems with PEITC is the recording of drug release times, profiles, and modeling for optimized administration. Attractively, from a physicochemical point of view, PEITC presents the appropriate characteristics to be formulated in a nanosystem, including stability.[160] Then, we will observe an increase in nanosystem studies with greater pharmacological efficiency. Mainly in the approach to cancer cells, nanosystems include evasion systems to increase the internalization of the cargo in the tumor and confer vectorization toward the damaged organ without altering other tissues.[73] For example, some studies presented in Table 4 mention the need for cellular internalization to increase ROS. The difference in the effect of PEITC alone and formulated in nanoparticles is also evident with statistical arguments.

7.2. Combinatorial Treatment for Synergistic Anticancer Effect of PEITC with Conventional Chemotherapeutic Drug or Radiotherapy

As mentioned above, PEITC has been found to have anticancer and chemopreventive effects against various kinds of cancers. This compound affects multiple cellular processes related to cancer growth, death, inflammation, blood vessel formation, and spread.[172,173] However, the clinical application of PEITC as a single agent may be limited by its low bioavailability, rapid metabolism, and potential toxicity at high doses. Therefore, it is vital to explore the potential of combining PEITC with conventional chemotherapeutic drugs or radiotherapy to improve its performance and safety for cancer treatment (**Table 5**). To our knowledge, the combination more studied in the literature is PEITC + cisplatin (a platinum-based drug). In a pioneer study, PEITC potentiated the cell death caused by different concentrations of cisplatin in NCI-H596 cells, a lung cancer cell line.[172] This effect was observed at both 10 and 20 μM doses of PEITC. According to the authors, the increased cytotoxicity was probably due to decreased expression of β-tubulin. Another study investigated the ability of PEITC to improve the cytotoxicity of cisplatin in cervical cancer (Henrietta Lacks cell line (HeLa) and C33A) and breast cancer (MCF-7) cell lines and the underlying mechanisms.[174] Pretreatment with PEITC potentiated the cell death induced by cisplatin; this effect was mediated by the upregulation of Noxa (a proapoptotic protein) and extracellular signal-regulated kinase (ERK) activation. Similarly, a recent study studied the effects of PEITC and cisplatinum in human cervical cancer cells

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Table 4. Examples of nanoformulations that include PEITC.

Type of nanosystem	Composition	Size [nm]	Cargo	Entrapment efficiency [%]	Model of evaluation	Effect	Reference
Metallic nanoparticle	Graphene oxide	6	PEITC	–	HepG2 cell line	↑antiproliferative activity decrease in IC_{50} from 7.5 to 2.5 μg mL^{-1} for PEITC without nanoparticle. The nanoparticles did not affect normal 3T3 fibroblasts.	[161]
Metallic nanoparticle	Au	97.5	PEITC	1.0024 mM (PEITC)	Hepatoprotective effect in the carbon tetrachloride (CCl_4)-induced damage in hepatocellular carcinoma G2 (HepG2) cell line	PEITC in nanoparticles had more hepatoprotective and antioxidant effects via Nrf2 activation against CCl4-induced liver injury in HepG2 cells	[162]
Protein	Albumin	100–200	PEITC+Paclitaxel	75 (Paclitaxel)	Subcutaneous mouse tumor	↑ protein-paclitaxel stability, blood circulation time, and tumor accumulation due to PEITC.	[163]
Protein	Albumin+PEG	185.6	PEITC	94.36	Antibacterial activity. Mouse infection model	↑ antibacterial activity against *S. aureus*, *B. subtilis*, *L. monocytogenes*, and *S. typhimurium*. Reduction of 15.2 folds bacterial viability in the area of infection.	[164]
Liposome	1,2-distearoyl-sn-glycero-3-phosphocholine and L-α-phosphatidylglycerol	130	PEITC+Cisplatin	1.37:0.80 (PEITC:Cisplatin)	NCI-H596 NSCLC cells	↑ cytotoxic activity against NCI-H596 NSCLC cells	[165]
Liposome	1,2-distearoyl-sn-glycero-3-phosphocholine and L-α-phosphatidylglycerol	140–170	PEITC+Cisplatin	37:83.9 (PEITC:Cisplatin)	Human non-small cell lung cancer A549, human lung adenosquamous carcinoma cell line H596	↑ cytotoxicity due to administration in liposomes and dual encapsulation.	[160]
Solid lipid nanoparticles	Stearic acid	158	PEITC, verapamil, nifedipine, tamoxifen	86.3 (PEITC)	Calu-3 cells	The IC_{50} value of PEITC decreases in combination with efflux inhibitors such as verapamil, nifedipine, or tamoxifen, increasing its chemotherapy efficacy.	[166]
Polymer-lipid	Hydroxyethyl starch-oleic acid conjugate	47.3	PEITC (solution pretreatment) +Indocyanine green(ICG)	84 (ICG)	Photodynamic therapy against HepG-2 human liver cancer cell line	↑intracellular ROS level ↑ the potency of photodynamic therapy	[167]
Polymeric micelle	Poly (ethylene glycol)-block-dendritic polylysine-PEITC-Paclitaxel(PTX). Third generation micelles	31	PEG-G3-PEITC/PTX	98.3 (PTX)	Subcutaneous and orthotopic human breast cancer xenografts	↓blood clearance ↑tumor accumulation ↑in vivo therapeutic efficacy PEITC in a third-generation micelle increases the release of paclitaxel against breast cancer	[168]
Polymer conjugate	Cinnamaldehyde-modified hyaluronic acid	166	PEITC	0.45% drug loading (PEITC)	Murine breast cancer (4T1 cells)	Superior antitumor efficacy by the enhancing oxidative stress of tumor cells ↑ROS, ↓GSH	[169]
Nanoemulsion	PEITC (Nanoemulsion) + Metotrexate (nanoparticles), hydrogel	240	PEITC+Metotrexate	83.16 (PEITC)	Rheumatoid arthritis animal model	↓chronic inflammation, ↓bone erosion, synovitis, control of inflammatory cytokine expression.	[170]
Quantum dots	Ag_2S	56	Ag_2S (adequate NIR-II imaging ability) + PEITC (solution)	–	Sonodynamic therapy against mouse tumor	↑ H_2O_2 content in tumor cells by producing O_2 catalyzed by the enzyme catalase. I ↑sonodynamic therapy to generate more ROS to inhibit tumor growth effectively	[171]

Abbreviations: Ag2S: Silver sulfide; CCl4: Carbon tetrachloride; GSH: Glutathione; HepG2: Hepatocellular carcinoma G2 cell line; ICG: Indocyanine green; NIR-II: Near-infrared Imaging II; NSCLC: Non-small cell lung cancer; PEITC: Phenethyl isothiocyanate; PEG: Polyethylene glycol; PEG-G3-PEITC/PTX: Poly (ethylene glycol)-block-dendritic polylysine-phenethyl isothiocyanate-paclitaxel; PTX: Paclitaxel; ROS: Reactive oxygen species. Symbols: ↑increase, ↓decrease.

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Table 5. Studies evaluating the synergistic effects of PEITC with conventional chemotherapeutic drugs or radiotherapy in different cell and animal models.

Combinatorial treatment	Cancer cells/animal model	Synergistic anticancer effects	Ref.
PEITC + Fludarabine	Chronic lymphocytic leukemia (CLL) cells isolated from patients	The combination of PEITC + fludarabine effectively killed fludarabine-resistant CLL cells. ↓GSH depletion, ↑ROS ↑ mitochondrial cardiolipin oxidation.	[188]
PEITC + Doxorubicin PEITC + Etoposide	Human prostate adenocarcinoa cell line (PC-3 cells)	PEITC sensitized PC-3 cells to undergo cell death by doxorubicin and etoposide. ↓antiapoptotic isoforms of PKC (α and ϵ) and telomerase.	[181]
	Cervical cancer cell line (HeLa) cells	PEITC sensitized HeLa cells to undergo apoptosis by doxorubicin and etoposide. ↓antiapoptotic isoforms of PKC (α, βII, ϵ, and ζ) and telomerase, ↑proapoptotic PKCδ	[182]
PEITC + Docetaxel	Cellular and xenograft (in mice) models of human prostate adenocarcinoma cell lines DU145 and PC-3	↑ apoptosis, ↑growth suppression induced by docetaxel in vitro. The combination was more effective against PC-3 xenograft than either agent alone. ↑Bax, ↑Bak, ↓Bcl-2 and XIAP protein levels.	[187]
	Human prostate cancer cell lines (PC-3 and DU145)	↑apoptosis ↑growth inhibition ↑interaction with microtubules, ↑modulation of androgens metabolism, ↑changes in GSH activity/levels ↑efflux transporters expression	[186]
PEITC + Cisplatin	Human non-small cell lung cancer lines (NCI-H596 cells)	↑cytotoxicity induced by different doses of cisplatin on NCI-H596 cells. ↓cellular β-tubulin	[172]
	Cervical cancer cell lines (HeLa and C33A) and breast cancer cell line (MCF-7)	↑apoptosis induced by cisplatin on all the cell lines. ↑Noxa, ↑ERK	[174]
	Cellular and xenograft (in mice) models of cisplatin-resistant cancer cell lines derived from non-small cell lung cancer (A549) and human colon cancer (THC8307)	synergistic effect in vitro and in vivo ↑apoptosis, ↓tumor growth. The effects were mediated by the depletion of GSH and subsequent increase of cellular platinum.	[176]
	Breast cancer cell lines (MCF-7 and MDA-MB-231)	synergistic anticancer activity, ↑apoptosis, ↓growth inhibition, ↑ cell cycle arrest in G2/M phases. ↑α-tubulin acetylation, ↑Bax, ↓Bcl-2 ↓Cdk1 expression	[184, 185]
	Human cisplatin-resistant gastric cancer cells (SGC7901/DDP cell line)	↑sensitivity to cisplatin, ↑apoptosis, ↑cell cycle arrest ↑ROS, ↑GSH depletion,↓P-glycoprotein expression, ↓MDR1 gene expression, ↓MRP1 protein expression, ↑Akt phosphorylation.	[177]
	Mesothelioma cell lines from pleural fluids of patients (nine lines)	↑cytotoxic properties and prevented the appearance of resistant cells. ↑damaging DNA, ↑apoptosis.	[179]
	Human hepatocellular carcinoma cell lines (HepG-2)	↑anticancer activity of cisplatinum ↑caspase-3 ↓ABCC2 transporter expression	[180]
	Cell lines and xenografts (in mice) Human cholangiocarcinoma (RBE) Human gallbladder cancer (GBC-SD)	↓ resistance to cisplatin in cancer cells ↑apoptosis rate in vitro ↓tumor weight in vivo. These effects were mediated by glutathionylation and subsequent degradation of Mcl-1.	[190]
	Human gastric cell lines (MKN45, AGS, MKN74 and KATO-III)	↑cisplatin anticancer effects, ↑G2/M cell cycle arrest, ↑apoptosis, ↑p53, ↓GSH	[178]
	Human cervical cancer cell lines (SiHa and SiHa^R) 3-methylcholanthrene-induced cervical cancer mice model	↑sensitivity to cisplatin ↓cell growth, ↓tumor size reduction. ↓GSH, ↓NF-κB, ↓phosphorylated Akt, ↓survivin, ↓XIAP, ↓MRP2, ↑ROS	[175]
PEITC + Doxorubicin	Osteosarcoma cell lines (U2-OS cells)	↑apoptosis induced by doxorubicin ↑caspase-3	[191]
	Cell lines of breast cancer (MCF-7) human hepatocellular carcinoma (HepG-2) Ehrlich solid tumor model in mice	↑ anticancer activity of doxorubicin, ↓tumor weight and volume in vivo ↓cell growth in vitro. ↑caspase-3, ↓Akt/NFκB	[183]

(*Continued*)

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Table 5. (Continued)

Combinatorial treatment	Cancer cells/animal model	Synergistic anticancer effects	Ref.
PEITC + Gefitinib	Non-small cell lung cancer cell lines (NCI-H1299 and SK-MES-1) in vitro and in vivo (xenograft in mice)	↑apoptosis rate ↑cell growth inhibition. ↑ER stress ↑ PERK-eIF2α-CHOP-Noxa ↓Mcl-1	[189]
PEITC + Ionizing radiation	Breast cancer cell lines (MCF-7)	↑sensitivity of MCF-7 cells to ionizing radiation, enhancing the efficacy of the cancer-killing method. ↑depletion of cellular GSH, ↑oxidative stress, ↑DNA damage, ↑cell cycle arrest, ↓cell viability	[173]

Abbreviations and symbols: ↑increase, ↓decrease, ABCC2: ATP binding cassette subfamily C member 2, Akt: Protein kinase B, Bax: Bcl-2-associated X protein, Bcl-2: B cell lymphoma-2, Cdk1: Cyclin-dependent kinase 1, CHOP: C/EBP-homologous protein, CLL: Chronic lymphocytic leukemia, eIF2α: Eukaryotic translation initiation factor 2α, ERK: Extracellular signal-regulated kinase, GSH: c-glutamate-cysteine-glycine, Mcl-1: Myeloid cell leukemia-1, MRP2: Multidrug resistance-associated protein 2, NF-κB: Nuclear factor kappa B, PEITC: Phenethyl isothiocyanate, PERK: Protein kinase RNA-like ER kinase, PKC: Protein kinase C, ROS: Reactive oxygen species, XIAP: X-linked inhibitor of apoptosis.

(SiHa and SiHaR) and a cervical cancer mice model induced by 3-methylcholanthrene.[175] PEITC improved the sensitivity to cisplatin in both experimental models, evidenced by inhibition of cell growth and tumor size reduction. The authors hypothesized that PEITC sensitized cancer cells by inhibiting the PI3K/Akt pathway and reducing the MRP2 expression. On the other hand, a resistance mechanism to cisplatinum is the elimination of the drug from the cells by GSH, which is elevated in cancer cells with stem-cell-like characteristics. A study used two human cancer cell lines that exhibited these features.[176] When combined PEITC and cisplatinum, they observed a potent anticancer effect both in vitro and in vivo. The combination induced more apoptosis, impaired cologny formation, and inhibited mouse tumor growth. The authors found that PEITC reversed this cisplatinum resistance by depleting GSH in the cells, which increased their platinum uptake and DNA binding. Gastric cancer is a major cause of death worldwide, and a common challenge is the development of resistance to cisplatin. Thus, a research group investigated whether PEITC can sensitize the gastric cancer cells SGC7901/DDP to cisplatin.[177] According to their results, PEITC can eradicate these cells by enhancing their susceptibility to cisplatin. PEITC induced cell death by various mechanisms, including increasing oxidative stress, depleting GSH, disrupting energy production, altering gene expression, and arresting the cell cycle. PEITC also modulated some pathways associated with drug resistance, such as Akt and NF-κB. Interestingly, similar results were described in a recent report.[178] Likewise, malignant pleural mesothelioma (MPM) is a deadly type of cancer that does not respond well to cisplatin, the current treatment. A remarkable study explored the effects of PEITC and cisplatinum in nine MPM cell lines derived from patients.[179] They found that this combination killed MPM cells in a concentration-dependent way. Another study explored the effects of PEITC on the cytotoxicity of cisplatin in human hepatocellular carcinoma cells (HepG2 cell line). The authors reported that PEITC potentiated the cytotoxicity of cisplatin by increasing the intracellular platinum levels and decreasing the expression of the ABCC2 transporter in the cells.[180] Collectively, these studies demonstrate that PEITC can enhance the anticancer effects of cisplatin by modulating various molecular pathways and mechanisms in several types of cancer cell types. Other treatments evaluated concomitantly with PEITC included doxorubicin, docetaxel, fludarabine, paclitaxel, gefitinib, and ionizing radiation. For example, Mukherjee et al.[181,182] evaluated the apoptotic potential of PEITC in combination with doxorubicin or etoposide in human prostate adenocarcinoma cells (PC-3) and cervical cancer cell line (HeLa). They found that pretreatment with PEITC sensitized both cancer cell lines to apoptosis by modulating PKC and telomerase expression. Thus, the authors concluded that the effect of PEITC could improve cancer therapy by reducing the dose of chemotherapeutic agents. In this regard, doxorubicin is also used to treat osteosarcoma, a malignant bone tumor. However, this compound has severe toxicities and can induce drug resistance in cancer cells. Thus, a study assessed whether PEITC can sensitize human osteosarcoma U2-OS cells to doxorubicin and enhance their apoptosis. The authors observed that PEITC and ADM alone reduced the viability and induced apoptosis of U2-OS cells dose-dependent, but their combination had a synergistic effect. Complementary experiments indicated that PEITC potentiated the anticancer effect of doxorubicin by inducing caspase-3-mediated apoptosis. The anticancer potential of PEITC in combination with doxorubicin has also been evaluated in human breast cancer MCF-7 cells and human liver cancer HepG-2 cells as in vitro models and Ehrlich solid tumor as an in vivo model.[183] PEITC and Dox doxorubicin enhanced the anticancer efficacy against breast and liver cancers by modulating key proteins and pathways involved in cancer progression and survival, such as Akt, NF-κB, caspase-3, and caspase-9. Thus, this combination therapy might be a promising strategy for clinical application.

On the other hand, Liu et al. investigated the effect of PEITC on the chemosensitivity of breast cancer cells to paclitaxel, a microtubule inhibitor.[184] They used two drug-resistant breast cancer cell lines, Michigan Cancer Foundation-7 (MCF7) and MDA-MB-231, as models. The combination of PEITC and taxol reduced the IC_{50} values of both agents in both cell lines, indicating a synergistic interaction. The combination also enhanced the apoptosis rate by more than twofold compared to each agent alone in both cell lines. It increased the percentage of cells

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in the G2/M phases, suggesting a cell cycle arrest. Concerning the possible mechanisms, the combination of PEITC and paclitaxel increased the acetylation of α-tubulin, a marker of microtubule stability, more than either agent alone. α-tubulin acetylation is associated with apoptosis induction and cell cycle arrest. Moreover, the combination of PEITC and paclitaxel modulated the expression of several proteins involved in cell survival, proliferation, and death. The combination decreased the levels of Cdk1 and B-cell leukemia/lymphoma-2 (Bcl-2), which promote cell cycle progression and inhibit apoptosis, and increased the levels of B-cell leukemia/lymphoma 2-associated X protein (Bax) and PARP, which trigger apoptosis.[185] Thus, the combination of PEITC and paclitaxel might be a potential strategy to overcome drug resistance in breast cancer.

Similarly, the effect of PEITC on the chemosensitivity of human prostate cancer cells to docetaxel has been evaluated in in vitro and in vivo models.[186,187] High concentrations of PEITC potentiated docetaxel-induced apoptosis in PC-3 and DU145 cells and the inhibition of PC-3 tumor growth in mice. PEITC synergized with docetaxel to induce more cytotoxicity than either agent alone. According to these studies, PEITC enhanced the anticancer effect of docetaxel by targeting different pathways and mechanisms, including downregulating Bcl-2 and XIAP proteins and upregulating Bax and Bak proteins.

Other research groups investigated the anticancer effects of PEITC in combination with gefitinib, fludarabine, or ionizing radiation in distinct cancer cell types.[173,188,189] PEITC and Gefitinib synergistically reduced the cell viability and increased the apoptosis and cell cycle arrest in non-small cell lung cancer (NSCLC) cell lines (NCI-H1299 and SK-MES-1) and significantly inhibited tumor growth in NCI-H1299 xenografts in nude mice.[189] PEITC enhanced the sensitivity of NSCLC cells to gefitinib by promoting the degradation of myeloid cell leukemia 1 (Mcl-1), an antiapoptotic factor, through the protein kinase RNA-like endoplasmic reticulum kinase (PERK)-eukaryotic translation initiation factor 2α-CHOP-Noxa pathway via posttranscriptional regulation. On the other hand, chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults, and it often does not respond to fludarabine-based treatments. In this regard, Trachootham et al. found that PEITC effectively killed fludarabine-resistant CLL cells isolated from patients.[188] PEITC treatment depleted GSH, increased ROS, reduced the expression and stability of Mcl-1, and impaired mitochondrial function in CLL cells, resulting in extensive apoptosis. Finally, radiotherapy is a treatment that kills cancer cells, but it can also harm healthy cells. A recent study described that PEITC enhances the cytotoxicity of ionizing radiation (5 Gy of X-ray radiation) on breast cancer cells (MCF-7).[173] Remarkably, PEITC only increased the radiosensitivity of breast cancer cells but protected normal breast cells from radiation damage; these effects were related to the GSH levels in the cells after treatment with PEITC. Since PEITC has a differential impact on breast cancer and normal breast cells, it may improve the outcome of radiation therapy.

In summary, evidence indicates that PEITC can synergize with cisplatin, doxorubicin, docetaxel, fludarabine, paclitaxel, gefitinib, or ionizing radiation to induce more pronounced apoptosis and growth inhibition in cancer than either agent alone (Table 4). The mechanisms underlying these synergistic effects may involve the modulation of drug transporters, DNA damage repair, antiapoptotic proteins, and cell cycle arrest.[175,182,183,185,190] Moreover, these studies suggest that PEITC could be used as an adjuvant therapy with conventional chemotherapeutic agents and radiotherapy. However, further studies are needed to confirm its efficacy and safety in animal models, and clinical studies will be required to support its therapeutic usefulness.

Figure 6 depicts the enhancement of standard cancer therapies by PEITC, suggesting a strategy for improved therapeutic outcomes.

8. Clinical Studies

In general, cruciferous vegetables are well-known to be enriched with isothiocyanates (R–N = C = S) responsible for their antitumor activity. The traditional use of these cruciferous vegetables as a PEITC source has many benefits in reducing cancer risk.[192] In different countries, various products of high PEITC content are now available in the market, such as powders or seeds of broccoli, as well as tea bags of watercress or radish. In addition, soups or beverages of watercress and broccoli have been widely used in their daily diet as detoxifying agents.[193,194] For instance, Portuguese individuals who consumed many fruits and vegetables, including broccoli and watercress, showed a significant survival of gastric cancer.[195]

Many epidemiological studies have confirmed the chemopreventive and chemotherapeutic efficacy of PEITC against different types of cancer[28] (**Table 6**). A questionnaire-based survey in China revealed that the continuous intake of dietary cruciferous vegetables reduces the breast cancer risk of Chinese women (age: 20–70 years).[196] Also, middle-aged Chinese men (age ± 65) showed a reduction in gastric cancer risk due to the high intake of cruciferous vegetables as determined by quantifying the urinary isothiocyanates and relating the results to GSTM1 and GSTT1 deletion with the enhanced protective effect of isothiocyanates.[197] Moreover, according to a questionnaire-based study, urinary bladder cancer patients improved survival in the USA due to their high intake of cruciferous vegetables.[198]

Likewise, traditional usage of available supplements containing PEITC (such as BrocElite plus (PEITC, Iberin, BITC and ATIC = 650 mg and stabilized Sulforaphane = 10 mg) and Benfida Puracress Pro (300 mg of watercress extract)) and efficient preclinical studies on the efficacy of this compound as an anticancer agent, stimulated their clinical assessment to prove their medical usefulness. Among different ongoing clinical trials, two studies were completed for their recruitment and on their way to posting their results. A phase II clinical study is on its way to evaluate the efficacy of PEITC (as watercress juice) on oral cells of heavy smokers with mutant p53, where p53 is a tumor suppressor gene expected to be mutant in smokers. This watercress juice is hypothesized to deplete this mutant p53 and act as an anticancer agent for oral cancers (www.ClinicalTrials.gov Identifier: NCT01790204). Also, researchers from National Cancer Institute, USA have established a randomized phase II trial to prove the efficacy of Broccoli sprout extract supplement (rich in PEITC) in slowing the growth of ductal carcinoma in women with breast cancer (www.ClinicalTrials.gov Identifier: NCT00843167).

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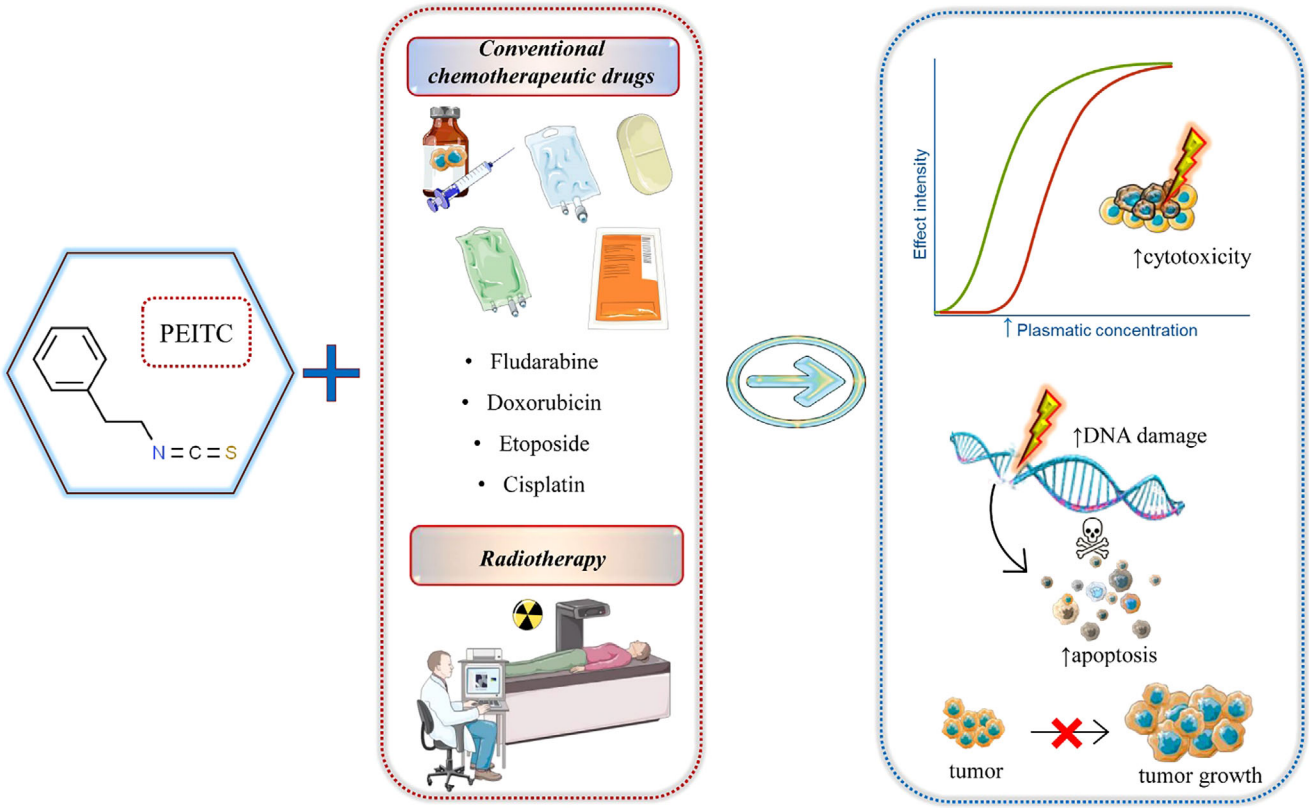

Figure 6. Synergistic effects of PEITC with chemotherapy and radiotherapy on cancer cell dynamics. PEITC, a compound derived from cruciferous vegetables, is known for its reactive N = C = S group that contributes to its anticancer properties. When combined with established chemotherapeutic agents such as Fludarabine, Doxorubicin, Etoposide, and Cisplatin, PEITC may enhance their cytotoxicity against cancer cells. The graph on the right demonstrates the correlation between increased plasmatic concentration of these compounds and the intensity of their combined effects, leading to escalated DNA damage and subsequent apoptosis in tumor cells. This therapeutic strategy also includes the additive benefits of radiotherapy, which, when used alongside PEITC and chemotherapy, could potentially lead to a reduction in tumor growth. The concerted action of these treatments is hypothesized to augment cancer cell death while mitigating the growth and proliferation of tumors. Symbols: ↑increase, ↓inhibition.

9. Therapeutic Perspectives, Clinical Gaps, and Challenges

9.1. Possible Explanations and Proposed Solutions for Disappointing Therapeutic Results of PEITC

One of the primary challenges with PEITC is its bioavailability. The absorption, metabolism, and elimination of PEITC can vary significantly among individuals, affecting its therapeutic efficacy. Genetic differences in metabolic enzymes can lead to variability in the systemic levels of PEITC, impacting its anticancer effects.[6] Future studies should focus on optimizing the delivery methods of PEITC to enhance its bioavailability. This could include the development of novel formulations or delivery systems like nanoparticles, liposomes, or conjugation with other molecules to improve stability and absorption.

The genetic background of the study population plays a critical role in the response to PEITC treatment. Genetic polymorphisms, particularly in genes related to detoxification and drug metabolism pathways (e.g., GSTM1, GSTT1), can influence the efficacy of PEITC.[199] Personalized medicine approaches should be considered, where genetic profiling of patients can guide the use of PEITC; stratifying patients based on their genetic makeup may help in identifying those who are most likely to benefit from PEITC treatment.[199]

PEITC interacts with a multitude of molecular pathways, and its anticancer effects can be influenced by the tumor microenvironment and the specific oncogenic pathways active in different cancer types.[200] A deeper understanding of the molecular mechanisms of action of PEITC is required. Comprehensive studies investigating the interaction of PEITC with various signaling pathways in different cancer types will aid in tailoring its use to specific cancer subtypes.[200]

The therapeutic effectiveness of PEITC is closely linked to its concentration. Both insufficient and excessive doses may lead to suboptimal outcomes. Rigorous dose-optimization studies are needed to establish the therapeutic window of PEITC. This should include investigations into the dose-response relationship in different cancer types and stages.

The diet of individuals can influence the effectiveness of PEITC. Other dietary components may interact with PEITC, potentially altering its anticancer properties. Dietary studies that consider the interaction of PEITC with other food components could provide insights into how diet can be optimized to support PEITC therapy.

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Table 6. Clinical trials of PEITC and their outcomes.

Clinical trial/study	Study subjects	Condition	Precursor lesions	Biomarkers for surrogate endpoint	Key findings/notes
NCT01790204	Heavy smokers	Oral cancer	Oral dysplasia	Mutant p53 levels, cellular changes in oral cells	Evaluating watercress juice in depleting mutant p53, hypothesized to act as an anticancer agent for oral cancers
NCT00843167	Women with breast cancer	Breast cancer	Ductal carcinoma in situ (DCIS)	Growth rate of DCIS, PEITC concentration in tissue	Assessing Broccoli sprout extract in slowing DCIS growth
[195]	Portuguese individuals	Gastric cancer	Not specified	Not specified	Significant survival benefit observed with high consumption of fruits and vegetables, including broccoli and watercress
[196]	Chinese women (age: 20–70 years)	Breast cancer	Not specified	Not specified	Continuous intake of dietary cruciferous vegetables linked to reduced breast cancer risk
[197]	Middle-aged Chinese men (age ± 65)	Gastric cancer	Not specified	Urinary isothiocyanates, GSTM1 and GSTT1 deletion	High intake of cruciferous vegetables associated with reduced gastric cancer risk
[198]	Urinary bladder cancer patients	Urinary bladder cancer	Not specified	Not specified	Improved survival with high intake of cruciferous vegetables

9.2. Toxicity and Safety Data

PEITC is a natural constituent of cruciferous vegetables and a common component of the human diet, which suggests its safety. However, the concentrations used for therapeutic purposes would likely exceed those obtained through dietary intake. In pharmacological studies, PEITC has demonstrated anticancer potential due to its possible ability to inhibit cancer cell growth and reverse multidrug resistance; however, the toxicity and safety profile of any bioactive compound are crucial for its development as a potential adjuvant chemotherapeutic agent. Animal studies have revealed that PEITC has a relatively low level of acute toxicity;[201] some studies have raised concerns over the potential genotoxicity of PEITC.[202] While some in vitro experiments have shown DNA damage at high concentrations, other research has shown no genotoxic effects in animal models.[202,203] High doses of PEITC can cause gastrointestinal irritation, leading to symptoms such as nausea or vomiting; also, there is evidence that PEITC might cause changes in liver enzymes in animal studies;[204] the clinical significance of these changes in humans is still under investigation. Early-phase clinical studies have evaluated PEITC as a potential anticancer agent, and it has generally been well-tolerated at doses used in these studies. Side effects have been mostly mild to moderate, including gastrointestinal disturbances.[56] The long-term safety of PEITC, especially at therapeutic doses, is not well-established. Chronic exposure to high levels of PEITC should be studied further to fully understand any potential adverse effects.

9.3. Limitations

While the cellular and molecular mechanisms of PEITC have been extensively studied in vitro, there is a notable lack of in vivo studies to validate these findings. The pharmacokinetic properties of PEITC remain not fully understood, posing challenges for determining optimal dosage and administration routes. Another concern is the potential cytotoxic effects of high concentrations of PEITC on normal cells, which raises questions about its safety profile. Additionally, the interaction of PEITC with other anticancer drugs or treatments has not been sufficiently investigated, potentially leading to adverse effects. Patient variability, including genetic and metabolic differences, can also lead to inconsistent responses to PEITC, complicating its clinical application. Regulatory hurdles exist, particularly as PEITC is a natural compound, making its path to clinical approval challenging. Lastly, the cost-effectiveness of isolating or synthesizing PEITC for therapeutic use remains an open question.

10. Conclusion

Dietary factors play a crucial role in cancer prevention, as evidenced by the growing literature on this topic. Among the nutritional constituents, PEITC, a compound abundant in cruciferous vegetables, has attracted attention for its potential as an adjuvant anticancer agent. PEITC has been used in traditional medicine and has demonstrated remarkable anticancer effects by modulating various cellular processes, such as survival and signaling pathways, apoptosis, cell cycle, and drug metabolism. The

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potential of PEITC as a natural adjunct to anticancer therapies opens new possibilities for integrative oncology, which combines natural and conventional medicine. Future research should focus on elucidating the molecular mechanisms and targets of PEITC action. Moreover, more clinical trials with diverse populations are needed to establish the safety and efficacy of PEITC in humans and to provide clear guidelines for its use. Likewise, future research should also explore the development of PEITC-based pharmaceuticals that can be standardized and optimized for therapeutic purposes. Collaboration between nutritionists, oncologists, and policymakers could lead to integrating dietary guidelines that emphasize the consumption of cruciferous vegetables, fostering a proactive approach to cancer prevention. Furthermore, individualized therapy based on metabolic profiles could enhance the effectiveness of PEITC-based treatments. In summary, the potential of PEITC as an anticancer agent is significant and promising but necessitates further robust scientific exploration. Fostering this natural compound's potential may lead to groundbreaking advancements in cancer treatment, offering an optimistic leap toward more effective, less toxic, and accessible therapeutic options.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

anticancer properties, apoptosis, cancer management, molecular mechanisms, phenethyl isothiocyanate, signaling pathways

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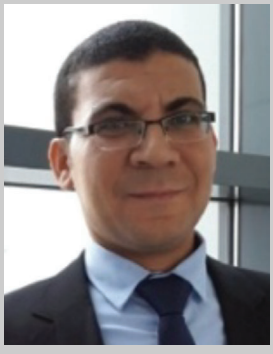

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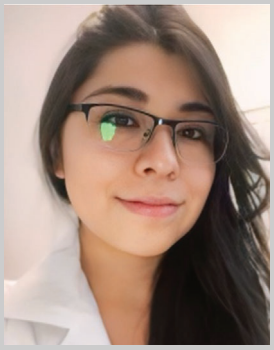

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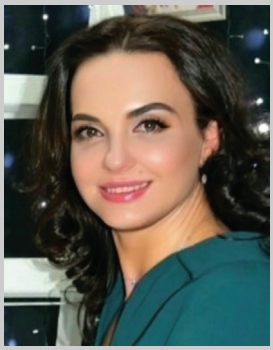

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