บทความ: สารฟังก์ชันเพื่อการป้องกันมะเร็งในระยะปฐมภูมิและตติยภูมิ

พื้นที่ที่นี้: สารฟังก์ชันเพื่อการป้องกันมะเร็งในระยะปฐมภูมิและตติยภูมิ

ปฐมภูมิ มองศิลป์ ดุลยพร ตราชูธรรม

หลักสูตรวิทยาศาสตรมหาบัณฑิตสาขาวิทยาศาสตร์พิษวิทยาและโภชนาการเพื่ออาหารปลอดภัย มหาวิทยาลัยมหิดล

สถาบันโภชนาการ มหาวิทยาลัยมหิดล

บทคัดย่อ

เฟเนทิล ไอโซไธโอไซยาเนต (พีอีไอทีซี) เป็นพืชเคมีในผักตระกูลกะหล่ำชี เช่น กะหล่ำปลี กะหล่ำปลี และคะน้า โดยพบว่า พีอีไอทีซีสามารถยับยั้งการเปลี่ยนรูปเป็นอนุมัติการก่อต้นของสารก่อมะเร็ง หลายชนิด การศึกษาในมนุษย์ยืนยันว่าสารก่อมะเร็งปลอดภัยในคนสุนัขได้ พีอีไอทีซีจัดเป็นสาร ป้องกันมะเร็งปฐมภูมิได้อย่างชัดเจนและ==='การก่อต้นของสารก่อมะเร็ง นอกจากนี้การวิจัยพบว่าสารก่อมะเร็ง เช่นแลกซิร์ และจะออกจากระยะปลอดภัยในสัตว์ทดลองได้ด้วยโดยจำเป็นต้องยับยั้งสูงได้โดยที่ไม่ให้มีเกิด ความเครียดต่อเนื่องในระยะต่อมา การศึกษาพบว่า พีอีไอทีซีอาจเป็นสารป้องกันมะเร็งได้ด้วยคือผลจากการ ดูดซับของโรค ซึ่งมักจะเกิดจากโรคระยะปลาย ซึ่งเป็นพืชเคมีขนาดต่างๆที่ใช้เป็นอาหาร นอกเหนือจากการขับออกไขมันอยู่ใน zar บางโรค ที่มีการใช้สารก่อมะเร็ง ซึ่งเป็นสารก่อมะเร็งภูมิ ไร้สารก่อมะเร็งในมนุษย์ไว้อย่างดี การศึกษาแสดงว่าสารก่อมะเร็งเช่นพีอีไอทีซีที่มีผลต่อ มะเร็งต่างๆ

คำสำคัญ: มะเร็ง เคมีป้องกัน พีอีไอทีซี สารก่อมะเร็ง
PEITC: Functional Compound for Primary and Tertiary Chemoprevention of Cancer

Patumrat Amornsil\textsuperscript{a} Dunyaporn Trachootham\textsuperscript{b, \ast}

\textsuperscript{a} Master Program in Toxicology and Nutrition for Food Safety, Mahidol University, Thailand
\textsuperscript{b} Institute of Nutrition, Mahidol University, Nakhon Pathom, Thailand

Abstract

Phenethyl isothiocyanate (PEITC) is a phytochemical found in cruciferous vegetables such as cabbage, watercress, and kale. Compelling evidences demonstrate that PEITC could both inhibit metabolic activation and activate phase II detoxification of several carcinogens. Clinical studies confirm its effect in reducing lung cancer carcinogen in tobacco smokers. The findings highlight PEITC as a primary chemopreventive agent to prevent the initiation of carcinogenesis. Interestingly, the very same compound PEITC also shows promising effects in selectively removal of cancer cells \textit{in vitro} and \textit{in vivo}. The anti-cancer mechanisms are mostly mediated through glutathione conjugation and redox balance shift toward increased oxidative stress leading to cell death. Those evidences raise PEITC as a new tertiary chemopreventive agent to retard progression of cancer. Toxicological studies showed that PEITC could induce bladder carcinogenesis if given at high concentration and long period. However, it is safe at 40 mg per day in human. This review summarizes the functional properties and roles of PEITC in primary and tertiary chemoprevention. Safety of PEITC is discussed. Further clinical investigations of PEITC are warranted to prove its primary and tertiary preventive effects in high-risk people and cancer patients, respectively, and evaluate long term safety and pharmacokinetic profiles in cancer patients.

\textbf{Keywords:} Cancer, Chemoprevention, PEITC, Cruciferous Vegetables, Carcinogen

\ast Corresponding author

Dunyaporn Trachootham
Institute of Nutrition, Mahidol University, 999 Phutthamonthon 4 Rd., Salaya, Phutthamonthon, Nakhon Pathom, 73170, Thailand Tel. 66-2-800-2380 ext. 326, Fax. 66-2-441-9344
E-mail: dunyaporn.tra@mahidol.ac.th; dunyaporn.tra@mahidol.edu
**Introduction**

Cancer is one of the most common cause of death worldwide \(^1\). Therefore, identifying effective cancer preventive strategies is crucial. Phytochemicals, bioactive compounds derived from plants remain one of the most studied cancer chemopreventive agents \(^2\). Among potent phytochemicals, Phenethyl isothiocyanate (PEITC) is a unique one with dichotomous properties of both detoxifying agent and pro-oxidant \(^3\). PEITC is a phytochemical found in cruciferous vegetables such as cabbage, watercress, and kale \(^5\). The compound has several advantages such as high bioavailability, high boiling point and easily released from vegetables upon chopping or chewing \(^6\). Importantly, PEITC shows promising effects in both primary and tertiary chemoprevention of cancer \(^3\). This paper reviews the functional properties and roles of PEITC in cancer prevention. Furthermore, safety information of PEITC has been discussed.

**Phenethyl isothiocyanate**

1. **Source, structure and bioavailability**

Phenethyl isothiocyanate (PEITC) is a phytochemical in cruciferous vegetables such as watercress, broccoli, cabbage, radish, Brussel sprout, cauliflower, kale etc. \(^4\). As shown in Figure 1, its structure is composed of aromatic ring, ethyl group and isothiocyanate (N=C=S) \(^7\). It is fat soluble compound with rapid absorption \(^9\). PEITC has bioavailability of at least 77% for single oral administration of 0.5 mg/kg body weight in rats \(^6\). The carbon atom in isothiocyanate part is highly electrophilic. Therefore, PEITC can readily conjugate with nucleophilic atoms such as nitrogen, sulfur and oxygen \(^7\).\(^10\). Thiol (sulfur) containing compounds such as glutathione and cysteine-rich proteins are attractive targets of PEITC \(^3\). Table 1 shows properties of PEITC.

![Figure 1. PEITC structure](image)
Table 1. Information and Physical property of PEITC

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<tr>
<td><strong>PubChem ID</strong></td>
<td>16741</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>163.24 g/mol</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>70 - 115%</td>
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<tr>
<td><strong>Solubility</strong></td>
<td>Fat soluble</td>
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<tr>
<td></td>
<td>Slightly water soluble (6.74x10^{-4} M)</td>
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<tr>
<td><strong>Molecular formula</strong></td>
<td>C_9H_9NS</td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>1.094 g/ml at 25 °C</td>
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<tr>
<td><strong>Boiling point</strong></td>
<td>278.1±19.0 °C at 760 mmHg</td>
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<td>139-140 °C at 11 mmHg</td>
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<td><strong>Biological activity</strong></td>
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<td></td>
<td><em>In vitro</em> antibacterial activity</td>
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<td></td>
<td><em>In vitro</em> and <em>in vivo</em> anti-proliferative activity against cancer</td>
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<td><em>In vitro</em> anti-oxidative stress</td>
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<td><em>In vivo</em> anti-carcinogenesis</td>
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<td><em>In vitro</em> and <em>in vivo</em> selective cancer cell death</td>
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<td><em>In vitro</em> and <em>in vivo</em> inhibition of tumor invasion and metastasis</td>
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<td><em>In vitro and clinical</em> inhibition of metabolic activation of carcinogen (phase I enzymes)</td>
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<td><em>In vitro and in vivo</em> Activation of phase II detoxification enzymes</td>
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<td>Glutathione conjugation and depletion</td>
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<td></td>
<td><em>In vitro and in vivo</em> increased oxidative stress</td>
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<tr>
<td></td>
<td><em>In vivo</em> reversible bladder carcinogenesis</td>
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<td></td>
<td><em>In vitro</em> inhibition of NF-KB activity</td>
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2. Formation of PEITC

PEITC is derived from hydrolysis of gluconasturtiin, a specific type of glucosinolates, by enzyme myrosinase (Figure 2). Usually, myrosinase is in a vacuole of plant. Although it requires hydrolysis of gluconasturtin for synthesis, cutting, chopping and grinding the plant can readily activate the enzyme and PEITC can be released. PEITC can be detected after grinding the cruciferous vegetable and hydrolysis is performed under controlled conditions of pH, time and temperature. The water-insoluble layer contains PEITC. Different species of cruciferous vegetables contains varied amount of PEITC with highest amount found in watercress. Heat treatment by steaming, microwaving and stir-frying did not induce significant changes in the contents of glucosinolates. In contrast, boiling could reduce the levels of glucosinolates in vegetables (approximately by 90%), by leaching into cooking water. Therefore, avoiding boiling of vegetables could increase the bioavailability of isothiocyanates including PEITC. Upon consumption chewing and gut flora can also activate myrosinase leading to the release of PEITC. Amount of bioavailable PEITC in blood can be detected by Liquid chromatography- mass spectrometry (LC-MS). Since extraction of PEITC from natural plants require controlled conditions of hydrolysis, most studies for biomedical applications utilized chemically synthesized PEITC. Recently, synthetic analogs of PEITC with structural modification has also been developed and their anti-proliferative activities were reported.

![Figure 2. Conversion of Gluconasturtiin to PEITC](image-url)
3. Metabolism and excretion of PEITC

The structure of PEITC contains electrophilic carbon thus readily conjugates with thiol group (-SH) especially in amino acid cysteine \(^7\). Therefore, PEITC is usually eliminated by conjugation with cysteine moiety of glutathione in liver catalyzed by gamma-glutamyltranspeptidase, cysteinylglycinase and N-acetyltransferase to be derivative of mercapturic acid, which was excreted with urine \(^9, 16\). N-acetylcysteine (NAC), an antioxidant and mucolytic agent \(^{20-21}\) can conjugate with PEITC through cysteine moiety and block its oxidative action \(^{21}\). To avoid excessive excretion of PEITC through conjugation with NAC, mucolytic drug containing NAC should not be consumed simultaneously with meal containing cruciferous vegetables.

Cancer chemoprevention

Cancer is a kind of disease that normal cells in body transform abnormally and have continuous proliferation until that area expands and is full of abnormal cells, called tumor \(^{22-23}\). There are two kinds of tumor including malignant and benign tumors. A malignant tumor is made up of cancer cells that mutate and can spread to other organs through blood or lymphatic circulation \(^{22-23}\). While a benign tumor is composed of normal cells which irregularly proliferate but do not metastasize to distant organs \(^{22-23}\). The evolution of cancer cells has many steps to develop from normal cell. Carcinogenesis includes three steps. First step is initiation. Normal cells are mutated after exposed to a carcinogen such as ionize radiation, UV radiation, smoking, red meat, asbestos, alcohol-derived acetaldehyde or viral infection \(^{22-23}\). The second step is promotion. The initiated cell is stimulated continuously by promotor agents or environment factors. Gene expression is altered until it uncontrollably proliferates. The last step, progression is a full transform step to be malignant tumor which poses invasive and metastatic potentials \(^{22-23}\). Carcinogens are substance driving initiation, promotion and progression of cancer \(^{24}\). Compelling evidences suggest that plant-derived compounds, phytochemicals play an important role in cancer prevention by blocking carcinogen or inhibiting steps of carcinogenesis \(^2\).
The hallmarks of cancer are cancer properties including sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, tumor-promoting inflammation, activating invasion and metastasis, inducing angiogenesis, genome instability and mutation, resisting cell death and deregulating cellular energetics 25.

As shown in Figure 3, primary cancer prevention is a method to decrease risk factors and incidence of disease before normal cells transform to pre-cancerous cells 26. Usually, primary prevention involves health promotion and avoidance of risk factors 26. Functional food blocking effects of carcinogens are considered primary chemopreventive agents 27. Secondary cancer prevention is aimed to inhibit alteration of pre-malignant or potentially malignant disorders (PMD) such as oral leukoplakia and colonic polyps to malignant diseases 26-27. Tertiary cancer prevention is sustaining stage after cancer diagnosis to break cancer cell growth and reduce violence of disease for continuous living with quality of life 26-27. Recently, quaternary cancer prevention has been proposed as “actions to identify patients at risk of overmedicalization, to protect him from new medical invasion, and to suggest ethically acceptable interventions”. The aim is to avoid unnecessary or excessive interventions 28.

![Figure 3. Multi-step carcinogenesis and cancer prevention](image-url)
Cancer preventive effects of PEITC

Numerous studies have demonstrated that PEITC can inhibit steps of carcinogenesis in several types of cancer including breast, prostate, oral, ovarian and lung cancer [3-4, 7, 8, 21, 29]. Existing literatures suggest the role of PEITC in primary and tertiary prevention as following.

1. Primary chemoprevention of cancer

The effect of PEITC in inhibiting carcinogens have been studied in animals and human.

1.1 In vivo

Several studies showed promising effects of PEITC in blocking both initiation and post initiation stage of carcinogenesis. For example, consumption of 5 μM PEITC for three weeks could prevent esophageal tumorigenesis induced by carcinogen N-nitrosomethylbenzylamine (NMBA) in rat [30]. Formation of hyperplastic and dysplastic lesions had been reduced by PEITC [30]. Consistently, another study using N-methyl nitrosourea (NMU) – induced breast cancerogenic model in rat found that treatment with 50 and 150 μmol/kg of PEITC every two days could reduce tumor incidence, multiplicity, angiogenic effects and increase time survival [31]. Likewise, treatment with 5 and 20 µM PEITC for eight weeks could reduce formation of azoxymethane (AOM) induced colonic aberrant crypt foci (ACF) [32]. Furthermore, when using combination of azoxymethane (AOM)-initiated and dextran sodium sulfate (DSS)-promoted colon carcinogenesis model 0.05% PEITC treatment for 20 weeks could also reduce tumor incidence, multiplicity and size of tumor in mice [33]. Mechanistic analysis revealed induction of cell cycle inhibitor p21 as a mechanism of cell cycle arrest and activation of caspase-3 and -7 in polyps as a mechanism of apoptosis [33]. PEITC was shown to reduce incidences of lung adenocarcinoma and multiplicities in rat model of lung cancer induced by tobacco-derived carcinogens - benzo(a)pyrene [B(a)P] and 4-Methylnitrosamino-1-3-pyridyl-1-Butanone (NNK) [34].

1.2 In clinical trial

The most well-studied effect of PEITC as chemopreventive agent is for tobacco-derived carcinogen. A clinical trial in smokers found that consumption of 10 mg PEITC in 1 ml of olive oil four times a day for five days could inhibit metabolic activation and induce excretion of NNK [35]. A follow-up study reported that PEITC can increase detoxification metabolites of benzene and acrolein in cigarette smoker with null genotypes of GSTM1 and GSTT1 genes [36].
1.3 Mechanism of action for primary chemopreventive effect of PEITC

Exposure to carcinogens and their metabolites can induce DNA damage, gene mutation and genomic instability which eventually drives transformation from normal cells to cancer cells. In most cases, phase I enzyme especially cytochrome P450 family catalyzes metabolic activation of procarcinogen to carcinogenic metabolites. Phase II enzymes such as glutathione-S-transferases (GST), N-acetyltransferases, and sulfotransferases conjugate with those metabolites to increase water solubility and promote excretion via urine or bile. Therefore, less phase I activities and more phase II activities may lower the effect of carcinogen and reduce risk of DNA damage. Interestingly, PEITC was shown to inhibit phase I enzyme such as CYP1 and activate Phase II enzymes such as GST. Furthermore, PEITC can increase gene expression of superoxide dismutase and glutathione peroxidase, which are detoxification enzymes. The roles of PEITC in detoxification of carcinogen are summarized in Figure 4.

Based on the existing in vivo evidences, it is likely that the effect of PEITC may not be only on primary chemoprevention but rather combination of primary and secondary chemoprevention. Nevertheless, the effect of PEITC as a sole secondary chemopreventive agent has not been reported. Further clinical studies in people with premalignant lesions such as oral leukoplakia and colonic adenoma are needed to evaluate the effect of PEITC in secondary chemoprevention.

2. Tertiary chemoprevention of cancer

The effects of PEITC on cancer cells in vitro and in vivo had been extensively studied. Molecular targets of PEITC involve multiple hallmarks of cancer such as apoptosis, proliferation, invasion and metastasis. The advantage of PEITC is its selectivity toward cancer cells than normal cells. Such property makes it attractive for clinical application with minimal side effects. Promising effect of PEITC against cancer stem cells, which is drug resistant population, makes it an attractive candidate for combination with conventional chemotherapy.
2.1 In vitro

PEITC has been shown to be selectively cytotoxic to a variety of cancer cell types. For example, PEITC was more cytotoxic to oral cancer cells than non-tumorigenic cells through ROS accumulation and activation of p53 and p21 at 5 µM PEITC. PEITC induced apoptosis and inhibited proliferation of cervical cancer cells by up-regulation of death receptors (DR4 and DR5) and inactivation of MEK/ERK pathway. In human chronic myeloid leukemia cell, PEITC can induce apoptosis by increasing caspase 9, 8 and 3 expression following the cytochrome c and increase ROS generation. Interestingly, 5 µM PEITC is effective in both fludarabine-sensitive and fludarabine-resistant chronic lymphocytic leukemia (CLL). The mechanism involves depletion of glutathione and increase oxidative stress; thereby, effective even in p53-deficient CLL cells. In prostate cancer cells, PEITC induced apoptosis, promoted G2/M cell cycle arrest via increased p21, caspase-3, 7 and Bax levels and reduced Cyclin B1 by Ras-association domain family 1 isoform A reactivation. Besides efficacy as single agent, combination between 4 µM PEITC and 3 µM doxorubicin (standard treatment for breast cancer) treatment enhanced apoptosis effectively and decreased HER2, EGFR and STAT3 in breast cancer cells with HER2 overexpression.
Cancer stem cell subpopulation usually plays role in drug resistance. PEITC decreased HER2 activation and sphere formation of HER2 overexpressed breast and ovarian cancer stem cells. Likewise, in Hela cancer stem cells PEITC suppressed aldehyde dehydrogenase 1 (ALDH1) cancer stem cell marker and SP1 transcription factor which play role in cell proliferation and cancer development. Numerous studies show effect of PEITC in suppression of cancer invasion and metastasis. For example, metastatic potential of lung cancer cell was inhibited by PEITC via inhibition of Akt/NFkB pathway. PEITC can inhibit adhesion, migration and invasion of human colon cancer cell through suppression of several signaling pathways such as SOS-1, PKC, ERK1/2 and Rho A.

**2.2 In vivo**

Effect of PEITC has been shown in several oncogenic transformed, natural-occurring cancer xenograft and transgenic models. For example, 50 mg/kg PEITC was shown to prolong survival time of mice bearing Ras-oncogenic transformed ovarian cancer xenograft by two-fold. PEITC suppressed tumor growth by EGFR/AKT inhibition and increased caspase-3 and apoptosis in natural occurring ovarian tumor xenografts. Furthermore, 12 μM PEITC decreased tumor volume by 76 % in mice with breast tumor xenograft. The mechanism involves suppression of myeloid derived suppressor cell (MDSCs) evidenced by decreased MDSCs markers (CD33+, CD34+, and CD11b+). MDSCs can down regulate T-cell function; therefore, inhibition of MDSCs can stop tumor growth. In brain metastasis model of breast cancer, giving 10 μM PEITC for 10 days could reduce spreading of breast cancer cells to brain by 50% and prolong survival of tumor bearing mice by 20.5 %. The mechanism involves HER2 suppression in brain. In mice bearing p53 mutated oral cancer xenograft, 5 and 10 mg/kg of PEITC reduced tumor growth and increased their survival times via cell cycle arrest by ROS generation and p53 reactivation. Likewise, in mice bearing glioblastoma cell xenograft 10 and 20 μmol/100 μL PEITC treatment for 21 days reduced tumor growth via suppression of MCL-1 and XIAP protein expression, and induction of caspase-3 and Bax expression. In d16HER2-transgenic mice model of breast cancer, synergistic effects between PEITC and trastuzumab (HER2 inhibitor) increased animal survival time.
2.3 Mechanism of action for tertiary chemopreventive effect of PEITC

Major anti-cancer mechanism of PEITC involves glutathione depletion and increased oxidative stress 3, 7, 55. Isothiocyanates (ITCs) including PEITC enter cells by passive diffusion and conjugate with sulfur atom in thiols moiety of glutathione (GSH) 55-56. Glutathione is major non-enzymatic antioxidant that protect cell from xenobiotic and oxidative stress 55. Amount of glutathione associate directly with ITCs uptake, ITCs conjugate with intracellular glutathione then eliminate glutathione out of the cells through multidrug resistance proteins (MRPs) 56-57 (Figure 5). The phenomenon results in glutathione depletion, which shifts redox balance toward increased oxidative stress, which could lead to cell death 3, 10, 58 (Figure 5) Several studies showed that glutathione tends to be elevated in cancer cells including breast, ovarian, head and neck and lung cancer 3, 19. Since the mechanism of cellular uptake and apoptotic induction by PEITC involves glutathione conjugation, the higher levels of glutathione in cancer cells may lead to higher uptake of PEITC in cancer cells than that of normal cells. This concept serves as a basis for selective cytotoxicity effect of PEITC against cancer 3, 10, 52. Besides the oxidative stress-mediated mechanism, a recent study proposed another selective mechanism of PEITC against cancer. The structure of PEITC contains electrophilic carbon which easily attacks nucleophilic atoms such as nitrogen and oxygen which are building blocks of DNA. PEITC was found to damage DNA in cancer cells more than normal cells because cancer cells are lacking of DNA repair mechanisms 59.

The mechanisms of PEITC in primary and tertiary chemoprevention seems to be conflicting. Some literatures have cited it as dichotomous role of PEITC 57. It could show both antioxidant and pro-oxidant properties depending on doses and cell types 3-4. Conjugation with glutathione could result in increased oxidative stress. At low doses, moderate stress can activate stress response pathway and induce NF-KB and NRF2 transcriptional factors, which consequently results in upregulated gene expression of antioxidant enzymes 57. At high dose, high stress can result in cellular damage especially if the cells already have high amount of ROS such as cancer cells 3-4.
Safety information of PEITC

The 0.9 - 1.2 µg/mL dose of PEITC was shown to be genotoxic to Chinese Hamster Ovarian cells by inducing DNA damage and mutagenesis. Furthermore, oral administration of 73 mg/kg PEITC (0.1% in diet) for 32-48 weeks altered bladder epithelium and induced carcinogenesis. Nevertheless, cessation of treatment can partly reverse the effect. Actually, such high dose and long period of administration could rarely occur because the effective doses of PEITC in most cancer preventive studies are much lower (5-10 mg/kg). Furthermore, several human studies using 40 mg PEITC for one week showed tolerability and safety in healthy volunteers. The same dose of 40 mg was shown to be effective in reducing tobacco-derived carcinogenic metabolite. Pharmacokinetic studies in healthy volunteers consistently showed that PEITC can be rapidly absorbed within few hours and excreted within 24 hours without accumulation effects. Therefore, up to 40 mg/ day of PEITC should be safe in human. However, clinical safety evaluation in long term such as several months warrants further investigation. Also, safety and pharmacokinetic profiles in cancer patients should be investigated.

Figure 5. Cellular uptake of PEITC and ROS-induced cell death
Conclusion

Figure 6 summarizes the complete chemopreventive mechanism of PEITC. Convincing evidences suggest that PEITC could be an effective primary and tertiary chemopreventive agent. The advantage of PEITC is in the selective toxicity against cancer and the efficacy in overcoming chemotherapeutic drug resistance. Although PEITC could be carcinogenic at high dose and longer period, its effective doses are still much lower than the toxic doses. Thus, further clinical investigations of PEITC in chemoprevention are warranted.

Conflicts of Interest

There are no conflicts of interest to declare for all authors.

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Figure 6. Complete chemopreventive mechanisms of PEITC
References


