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Review

Phenethyl isothiocyanate: A comprehensive review of anti-cancer mechanisms

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ABSTRACT

The epidemiological evidence suggests a strong inverse relationship between dietary intake of cruciferous vegetables and the incidence of cancer. Among other constituents of cruciferous vegetables, isothiocyanates (ITC) are the main bioactive chemicals present. Phenethyl isothiocyanate (PEITC) is present as gluconasturtiin in many cruciferous vegetables with remarkable anti-cancer effects. PEITC is known to not only prevent the initiation phase of carcinogenesis process but also to inhibit the progression of tumorigenesis. PEITC targets multiple proteins to suppress various cancer-promoting mechanisms such as cell proliferation, progression and metastasis. Pre-clinical evidence suggests that combination of PEITC with conventional anti-cancer agents is also highly effective in improving overall efficacy. Based on accumulating evidence, PEITC appears to be a promising agent for cancer therapy and is already under clinical trials for leukemia and lung cancer. This is the first review which provides a comprehensive analysis of known targets and mechanisms along with a critical evaluation of PEITC as a future anti-cancer agent.

Contents

Abbreviations: BaP, Benzo(a)pyrene; BCRP, Breast Cancer Resistance Protein; CSC, Cancer Stem cells; ECS, Environmental Cigarette Smoke; GPX, Glutathione peroxidase; GSH, Glutathione; GST, Glutathione S-transferase; HBEC, Human Bronchial Epithelial Cells; HBP, 4-hydroxy-1-(3-pyridyl)-1-butanone; ITC, Isothiocyanate; NAC, N-acetyl cysteine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PEITC, Phenethylisothiocyanate; Rb, Retinoblastoma protein; ROS, Reactive oxygen species; DDB2, DNA-damage binding protein 2

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1. Introduction

Since prehistoric times, nature has been a rich source of many drugs and drug leads, which are currently being used to treat various ailments, including cancer. According to Newman and Cragg, 74.8% of present anticancer agents originated from natural sources, with almost 48.6% being the actual natural compound or a direct derivative [1]. These include several widely used anticancer agents like taxanes, vinca alkaloids and camptothecin class of compounds. Interest in natural products as an alternative to synthetic drugs for cancer treatment is largely due to low cost, established historical use in traditional medicinal systems, easy availability and minimal or no toxicity. Also, the potential for targeting multiple pathways represents an advantage of natural compounds over synthetic agents, the latter being more target-specific.

Cancer is a complex manifestation of genomic instability in cells caused by environmental or genetic factors [2]. Genomic instability leads to disruption of basic biological functions, such as cell division, differentiation, angiogenesis and migration, which promote cancer [2]. The involvement of multiple mechanisms in cancer development raises an urgent need for multi-targeted therapy. The current anti-cancer agents primarily focus on specific targets. The suppression of unique targets usually leads to activation of compensatory mechanisms resulting in failure of therapy or development of resistance to drugs. To circumvent these problems, combination therapy is currently employed by the oncologists. Nonetheless, combination approach has also shown marginal advantage in the overall therapy due to development of resistance or associated toxicity. We have reached a threshold in terms of clinical benefit and tolerance in patients.

Of all the isothiocyanates (ITCs), phenethylisothiocyanate (PEITC) is the only one that has reached the clinical stage of testing. This review provides a critical and comprehensive analysis of the outcomes of studies showing the anti-cancer effects of PEITC.

2. Epidemiological evidence for chemo-preventive effects of dietary intake of cruciferous vegetables

Several epidemiological studies from different parts of the world provide a strong evidence for the reduced risk of cancer with higher intake of cruciferous vegetables [3–7]. Although none of these studies provide a direct correlation between cancer incidence and intake of a specific ITC, many studies do identify a correlation between the total ITC intake in the form of cruciferous vegetables and reduced risk of several types of cancers in lung, breast, gastric, bladder, colorectal, pancreatic, prostate and kidney (Table 1) [5,8–27]. Interestingly, there are also few studies where the results obtained were opposite to the preventive effects of cruciferous vegetables. For example, depending on the duration of intake and age of subjects, one of the studies has shown differential effects of cruciferous vegetables [20]. In a prospective study, Giovannucci et al. did not observe any significant correlation between prostate cancer risk and a short-term intake of cruciferous vegetables [20]. However, long-term intake of cruciferous diet showed a stronger inverse correlation with initial stages of prostate cancer and this effect was stronger in men less than 65 years of age [20]. In contrast, a few other studies reported no correlation between the intake of cruciferous vegetables and cancer incidence [27]. The differences in the outcome showing no correlation with dietary intake of cruciferous vegetables could be due to several confounding factors such as, differences in the subject population, duration of intake of cruciferous vegetables in subject's lifetime, age of subjects, variation in the isothiocyanate content in cruciferous vegetables based on geographic locations and whether the consumed vegetables were raw or cooked. Out of 22 studies performed, one study showed increased risk of thyroid cancer with ITC intake, while three studies (urinary, prostate and breast cancers) showed no correlation of ITC intake with cancer incidence. Interestingly all the studies on stomach, colon and lung cancers showed reduced cancer incidence with ITC intake. A detailed analysis revealed that studies showing no correlation between ITC intake and cancer incidence typically had wider trial durations or greater age differences for the subjects. Interestingly, a study performed in 2001 showed a significant change in people's food habits and lifestyle over the last decade [28]. Hence, the outcomes from studies performed in the last decade might be affected due to these confounding factors. Furthermore, the majority of the findings were based on questionnaires for the intake of cruciferous vegetables, which can have lot of variability. In most of the studies, questionnaires were not specific in asking whether the vegetables were raw or cooked.

However, based on the majority of the studied outcomes, we can conclude that an inverse relationship exists between intake of ITCs in the form of cruciferous vegetables and the overall incidence of cancer. But no conclusion can be drawn with respect to any specific isothiocyanate at this time.

3. PEITC source and pharmacokinetics

3.1. Cruciferous vegetables—source of PEITC

The isothiocyanates (R–N = C = S) (ITC) are known to be the major bioactive compounds present in cruciferous vegetables and responsible for anti-cancer activity. ITCs are released from glucosinolates by the action of the enzyme myrosinase. The enzyme myrosinase can be activated by cutting or chewing the vegetables, but heating can destroy its activity [29]. However, microbial myrosinase from gut can also release ITCs in the stomach after ingestion of cruciferous vegetables [30,31]. Studies show that myrosinase as well as isothiocyanates are thermolabile [32]. Hence ingestion of only raw vegetables can release ITCs and cooking of the vegetables can reduce ITC content [32]. Although water cress and broccoli are known to be the richest source, PEITC can also be obtained from turnips and radish. PEITC is present as gluconasturtiin in cruciferous plants. Like other ITCs, PEITC can be released from gluconasturtiin by the action of myrosinase [30,31]. In a study conducted with human volunteers, approximately 2 to 6 mg of PEITC was found to be released by the consumption of one ounce of watercress [33,34].