ความปลอดภัยทางคลินิกของเจลลี่โภชนาผสมสารพีอีไอทีซี: การศึกษาแบบก่อน-หลัง ในอาสาสมัครสุขภาพดี

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บทคัดย่อ

เบต้าเฟนทิลไอโซไธโอไซยาเนต (พีอีไอทีซี) เป็นพฤกษเคมีที่กระตุ้นการกำจัดสารก่อมะเร็ง และยับยั้งการแบ่งเซลล์มะเร็ง เจลลี่โภชนาผสมพีอีไอทีซีเป็นอาหารเจลที่ให้ทั้งสารอาหารและประโยชน์ต่อสุขภาพ การศึกษาเภสัชจลนศาสตร์และความทนนาน 5 วัน พบว่าดูดซึมเร็วและกำจัดหมดใน 24 ชั่วโมงไม่มีการสะสมของพีอีไอทีซี แต่ยังขาดข้อมูลความปลอดภัยระยะยาว การศึกษาแบบก่อน-หลังนี้ทำเพื่อทดสอบความปลอดภัยของการรับประทานเจลลี่โภชนาผสมพีอีไอทีซีวันละ 200 กรัม (มีพีอีไอทีซี 20 มิลลิกรัม) ต่อเนื่อง 35 วัน ในคนสุขภาพดี 12 คน (ชายและหญิงอย่างละ 6 คน) อายุเฉลี่ย 29.3±5.8 ปี โดยประเมินผลที่ 0, 1, 3 และ 5 สัปดาห์หลังรับประทาน และ 2 สัปดาห์หลังหยุดรับ ผลการศึกษาพบอาการไม่พึงประสงค์แบบไม่รุนแรงและหายเองได้ ร้อยละ 16 ได้แก่ ระคายเคืองในช่องปาก และท้องอืด ค่าความสมบูรณ์ของเม็ดเลือด การทำงานของตับไต และเคมีคลินิกเปลี่ยนแปลงเล็กน้อย แต่อยู่ในเกณฑ์ปกติ โดยฮีมาโตคริตลดลงหลังรับประทานเจลลี่ 3 สัปดาห์ จากนั้นกลับเท่าค่าเริ่มต้น กรดยูริกลดลงหลังรับประทานเจลลี่ 5 สัปดาห์ แต่กลับเท่าค่าเริ่มต้นเมื่อหยุดรับ เกล็ดเลือดไม่เปลี่ยนแปลงในช่วงรับประทานเจลลี่ แต่เพิ่มขึ้นในช่วงหยุดรับ อาสาสมัครทุกคนรับผลิตภัณฑ์ครบ ไม่มีใครออกจากการศึกษาก่อนกำหนด โดยสรุปการบริโภคเจลลี่โภชนาผสมพีอีไอทีซี ซึ่งให้พีอีไอทีซีวันละ 20 มิลลิกรัม ต่อเนื่อง 35 วัน ไม่ก่อเหตุการณ์ไม่พึงประสงค์

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Clinical Safety of Nutri-PEITC Jelly: A Pre-Post Study in Healthy Volunteers

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Abstract

β-phenylethyl isothiocyanate (PEITC), a phytochemical, promotes the detoxification of carcinogen, and inhibits the proliferation of cancer cells. Nutri-PEITC Jelly is a food gel providing both nutrients and functional benefits. Pharmacokinetics and 5-day tolerability studies revealed rapid absorption and excretion of PEITC in Nutri-Jelly within 24 hours without accumulation. However, information on the long-term safety of Nutri-PEITC Jelly is lacking. This pre-post study was conducted to evaluate the safety of 200 g Nutri-PEITC Jelly (giving 20 mg PEITC) daily intake for 35 days in 12 healthy volunteers (6 male and 6 female, average age 29.3±5.8 years old). All outcomes were measured at 0, 1, 3, and 5 weeks after Nutri-PEITC Jelly intake, and also 2 weeks after stopping the jelly intake. The results showed adverse events found in 16% of participants including oral discomfort and abdominal bloating. All symptoms were mild, transient, and subsided without treatment. Complete blood count, liver and kidney functions, and clinical blood chemistry slightly changed but within the normal ranges. The average level of hematocrit was significantly decreased after 3 weeks of intake but resumed afterward. The average level of uric acid was reduced after 5 weeks of intake but resumed after stopping the intake. The average platelet counts did not change during the intake period but increased after stopping the intake. All participants completed the study with no drop-outs. In conclusion, our results demonstrate no significant adverse events of Nutri-PEITC Jelly (containing 20 mg PEITC) after 35-day intake.

Keywords: PEITC, Nutri-Jelly, Phytochemical, Safety, Nutrition, Clinical study

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Introduction

β-phenylethyl isothiocyanate (PEITC) is a phytochemical bioactive compound with several biological properties and naturally present in cruciferous vegetables such as watercress, broccoli, wasabi and cabbage[1]. PEITC can inhibit phase I enzymes, including the various type of cytochrome P450 (CYP) enzymes. In addition, PEITC can also induce phase II detoxification enzymes, including glutathione *S*-transferase (GST) and quinone reductases that inactivate carcinogens and promote their excretion[2-4]. Therefore, PEITC exerts cancer chemoprevention activity[2,5]. Moreover, anti-cancer effects of PEITC have been studied and showed promising results in several types of cancer, including cancers of head and neck, ovary, lung and breast[6-9]. Anti-cancer effects of PEITC mainly involve generation of reactive oxygen species which lead to cell cycle arrest, autophagy, and/or apoptosis, among other mechanisms[6]. Previous studies showed that PEITC can selectively kill cancer cells with minimal or no side effects to normal cells, which have lower baseline oxidative stress[7,10-12]. In vivo studies also supported its anti-cancer effects in several cancers, including head and neck cancers[13-15]. Previous study showed that PEITC at 5 and 10 mg per kg body weight can slow down the tumor growth and prolong the survival in oral cancer-xenograft mouse model[10].

Head and neck cancers are among one of the most common cancer worldwide[16]. Due to its location, the cancer itself as well as the treatment, including surgery, radiotherapy and chemotherapy, adversely affect patients' ability to eat and swallow. Head and neck cancer patients eventually suffered from malnutrition leading to poor treatment outcome[17,18]. The current management for head and neck cancer patients, therefore, include multidisciplinary approach which involves medical oncologists, nurses, dietitians, dentists, social workers, occupational therapists and palliative care specialists, in order to provide the best care and improve quality of life for the patients[19].

Ability to eat and swallow through the mouth was strongly associated with quality of life and was one of the predictor for survival of head and neck cancer patients[17]. The Dental Innovation Foundation under Royal Patronage, which is a non-profit organization, has developed and formulated the food gel with semisolid texture called "Nutri-Jelly". Nutri-Jelly is a ready-to-eat nutritious gel with 260 kcal per serving (Figure 1). The product has been approved by Thai Food and Drug Administration and was shown to be edible and well-accepted by head and neck cancer

patients. Continue use of this product was shown to improve health-related quality of life and reduce tube feeding demand in head and neck cancer patients[20].

To expand the utilization of Nutri-Jelly, the Dental Innovation Foundation under Royal Patronage furthered their research by combining nutritional support with PEITC for potential use as chemo-preventive or chemotherapeutic tools for cancers. The Nutri-PEITC Jelly was tested and proved to be safe in animal model for acute and sub-acute toxicity (unpublished results). In addition, safety, tolerability as well as pharmacokinetics after a single and multiple 5-day oral doses of Nutri-PEITC Jelly containing 40 mg PEITC per day in healthy volunteers have been investigated and demonstrate acceptable safety profile and minimal accumulation index[21]. However, the dose conversion from our *in vivo* efficacy study for anti-cancer effects[10] and the human sensory acceptable concentration of PEITC in Nutri-Jelly (unpublished data) yielded the dose of 20 mg PEITC in a 200 g box of Nutri-jelly. Thus, this study was aimed to evaluate clinical safety of 20 mg of PEITC in Nutri-Jelly in healthy volunteers after 35-day administration.

Figure 1. Nutri-Jelly demonstrates semisolid texture and is packed in a sealed container

Materials and Methods

This study was performed in accordance with the principles of Good Clinical Practice (GCP). The research protocol was approved by the Ethics Committee of the Faculty of Dentistry, Srinakharinwirot University (protocol review no. SWU 5/2557). All subjects were informed about the potential risks in participating in the study and provided written informed consents before enrollment.

Subjects

Inclusion criteria of the study population included 12 healthy male and female aged 20-45 years old, weighed 35-65 kg, had BMI between 18-23 kg/m^2, and did not take acetaminophen within 1 week before enrollment. The healthy stage of the subjects were evaluated by physical examination and clinical laboratory tests (hematology, lipid profile, fasting blood sugar, liver and renal function tests). Subjects who were pregnant or breastfeeding, had oral ulcer or other oral mucosal problems were excluded from the study. The subjects can opt out from the study anytime as they wished or if they were unable to come back for the follow up visit, allergic to PEITC, developed abnormal blood results or other side effects after taking Nutri-PEITC Jelly.

Sample size

There are no standard guidelines on the sample size for clinical safety tests of food products. However, the guideline for designing phase 1 clinical trial to evaluate the safety of drugs usually recommended no more than 20 subjects[22]. Our previous pharmacokinetic and short-term tolerability test utilized 12 participants[21], which is similar to several other studies for the safety of food supplement products[23-26]. Therefore, we also used 12 subjects in this work. To ensure that our data have adequate statistical merit, we calculated the post-hoc power of the primary outcome measure which is the laboratory value. Using the hematocrit data, we obtained the post-hoc power of 0.85.

Nutri-PEITC Jelly preparation

Nutri-PEITC Jelly was manufactured through Ultra High Temperature (UHT) processing and filled aseptically in a sealed box by the Dental Innovation Foundation under Royal Patronage. The product passed microbiological tests from outside certified laboratory according to regulation of food in hermectically sealed container. Each box of 200 g Nutri-PEITC Jelly contained 20 mg (0.01% w/w) food-grade PEITC ($C_6H_5CH_2CH_2NCS$, Sigma-Aldrich, MO, USA) and was stored at room temperature. The 20 mg PEITC dosage was calculated based on equivalent mouse dose with anti-cancer effects from in vivo study[10]. In addition, this dose (0.3-0.6 mg/kg for consumers weighed 35-65 kg) was much lower than lethal dose 50 (LD50) of Nutri-PEITC Jelly tested in mouse (more than 15,000 mg/kg) (unpublished results).

Study design

All subjects were required to take one box of Nutri-PEITC Jelly (20 mg of PEITC)

in the morning every day for 5 weeks. After one week, the subjects were asked to come for follow up visit to evaluate the adverse effects and tolerability to the Nutri-PEITC Jelly. Blood sample collection was performed to investigate the changes in clinical laboratory value at 1, 3 and 5 weeks after Nutri-PEITC Jelly ingestion and also 2 weeks after the subjects stopped taking Nutri-PEITC Jelly. A 7-week study design was modified from previous studies[23,27]. The subjects were asked to abstain from food or drink for 12 hours before the blood collection. The clinical laboratory values investigated included red blood cell counts (RBC), white blood cell counts (WBC), hematocrit, fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine, uric acid, cholesterol (total, high-density (HDL) and low-density (LDL) cholesterol) and liver enzymes (SGOT and SGPT). The laboratory assays were performed by Prolab, a certified clinical laboratory. The subjects were asked to record daily intake of Nutri-PEITC Jelly and side effects. Also, they were asked to notify the researchers if they drank alcohol or took acetaminophen. No diet restriction was requested. Detail of adverse events and abnormal laboratory values, including severity, duration, relationship to the study and the management, were monitored throughout the study by subject interview and clinical evaluation by physician.

Statistical analysis

The clinical information of the subjects, laboratory values as well as data from adverse event record form were collected and transferred to electronic record form without subject identification. Demographic data and adverse events were reported using descriptive statistics. IBM SPSS program was used for statistical analysis. Comparison of each clinical laboratory parameter among various time points was performed by using Friedman's test. A p-value of less than 0.05 was considered statistically significant. Post-hoc power was calculated by using G-Power Version 3.1.9.2.

Results

Demographic data of study population

A total of 12 healthy subjects (6 males and 6 females) were enrolled in the study. The mean ± SD age of the subjects was 29.3±5.8 years, ranging from 21-36 years old. Mean weight and height of the study subjects were 56.5±5.4 kg and 160 ± 10 cm, respectively, with a calculated mean BMI of 20.9±1.6 kg/m^2, ranging from (18.8-23). All 12 subjects finished the study, leaving 0% dropped out rate. Compliance was 100% in 11 subjects and the other 1 subject missed 2 doses of Nutri-PEITC.

Adverse events

Adverse events reported were mild and reversible. In addition, each symptom affected only 1-2 subjects as shown in Table 1. Some side effects may be related to the pungent test and smell of PEITC, such as loss of appetite and rough tongue feeling. Other gastrointestinal symptoms, such as abdominal bloating and nausea, may not be directly related to PEITC but the high energy Nutri-Jelly itself or other causes. Moreover, other symptoms, such as diarrhea and dizziness, were reported but the symptoms were transient and resolved spontaneously.

Clinical Laboratory data

As shown in Table 2, all average clinical laboratory values, including hematology, blood chemistry levels, kidney and liver function tests, were within normal limits during the 5 weeks of Nutri-PEITC Jelly intake as well as 2 weeks after discontinuation of Nutri-PEITC Jelly. There were statistically significant differences in laboratory values between baseline and follow up visits in some parameters (hematocrit, platelets and uric acid). However, the values were still within normal ranges and no clinical abnormalities were observed by physical examination. The results, therefore, were interpreted as normal fluctuation.

When considered each subject separately, we found subjects with increased liver enzymes on week 3 of Nutri-PEITC Jelly intake (1 subject) and 2 weeks after Nutri-PEITC Jelly administration (2 subjects), which correlated with alcohol intake. The values of liver enzymes in those subjects were normal in other time points. Also, minimal decrease in white cell counts was noted in 1 subject on week 3 and another subject at 2 weeks after finished taking Nutri-PEITC Jelly. Moreover, one subject showed an increase in total cholesterol (255 mg/dl) and LDL (172 mg/dl) from baseline (185 mg/dl total cholesterol and 125 mg/dl LDL) on week 5 of Nutri-PEITC Jelly intake. Nevertheless, the total/HDL ratio was within normal range (4, less than 5) and the values were normal in other time points. All these changes were not clinically significant and were considered less likely to be related to Nutri-PEITC Jelly. The summary of the results are shown in Table 3.

Table 1. Adverse events reported by the subjects

Adverse events	N	%	Additional information	Management	Outcome
Abdominal bloating	2	16	Occurred only when took with empty stomach	Advised to avoid taking with empty stomach	Symptom disappeared
Nausea	1	8.33	Occurred only when took with empty stomach	Advised to avoid taking with empty stomach	Symptom disappeared
Loss of appetite	1	8.33	Started at week 4	Advised to drink water or mouthrinse with water	Mild symptom persisted from week 4-5 when took the jelly. Reversible when stopped taking the jelly.
Rough tongue feeling	2	16	Feeling rough at dorsal surface of tongue	Advised to drink water or mouthrinse with water	Symptom disappeared in 1 hour for 1 subject. Mild symptom persisted when took the jelly for 1 subject. Reversible when stopped taking the jelly.
Dizziness	1	8.33	Mild symptom. Occurred on day 1 and 2	Observation	Symptom disappeared No additional management required
Diarrhea	1	8.33	Occurred for 1 day at week 2	Observation	Symptom disappeared No additional management required

Table 2. Average clinical laboratory values at baseline, during and after Nutri-PEITC Jelly intake*

Parameters	Baseline	First week	Third week	Fifth week	Two weeks after
Weight (kg)	56.5±5.4	56.9±5.7	56.63±5.92	56.98±6.16	56.98±6.18
Hct (%)	39.8±2.3	38.3±3.0	37.92±3.42*	38.08±2.31	39.92±3.23
WBC ($x10^3$ cells/ml)	6.4±1.5	6.2±1.3	5.5±1.5	5.5±0.9	5.7±1.8
RBC ($x10^9$ cells/ml)	5.1±0.5	4.76±0.67	4.89±0.45	4.91±0.49	4.84±0.34
Platelet ($x10^7$/ml)	30.1±5.85	29.1±6.7	28.4±6.7	28.3±5.4	31.6±11.5*
BUN (mg/dl)	11.4±2.2	11.58±3.32	11.00±2.56	11.42±3.26	11.00±2.37
Creatinine (mg/dl)	0.9±0.1	0.92±0.09	0.91±0.12	0.93±0.20	0.88±0.11
Uric acid (mg/dl)	5.7±1.2	5.26±1.19	4.92±1.19	4.73±1.35*	4.79±1.04
SGOT (mg/dl)	26.5±4.0	28.25±5.64	29.58±6.11	27.67±5.10	32.33±9.28
SGPT (mg/dl)	22.8±3.9	26.25±9.08	26.33±6.80	26.83±7.00	28.83±10.09
Triglyceride (mg/dl)	83.3±9.1	90.25±15.56	91.92±20.02	86.17±15.53	85.33±15.10
Cholesterol (mg/dl)	186.8±8.7	196.33±15.32	198.75±21.61	193.67±22.01	193.00±13.60
HDL (mg/dl)	48.6±4.6	51.25±4.99	52.00±5.36	50.08±4.27	49.50±4.08
LDL (mg/dl)	121.4±10.2	127.17±9.68	128.42±14.33	126.50±16.34	126.50±9.18
Total/HDL	3.9±0.4	3.84±0.26	3.83±0.23	3.86±0.20	3.91±0.22
Fasting Blood Sugar (mg/dl)	85.1±5.5	84.58±4.06	81.25±4.09	83.67±5.23	87.17±6.49

* indicates $p < 0.05$, compared with baseline values of each parameter

Table 3. Numbers of subjects with abnormal laboratory values at baseline, during and after Nutri-PEITC Jelly intake

	Baseline	First week	Third week	Fifth week	Two weeks after
Weight (kg)	0	0	0	0	0
Hct (%)	0	0	0	0	0
WBC ($x10^3$ cells/ml)	0	0	1 (3600)	0	1 (3800)
RBC ($x10^9$ cells/ml)	0	0	0	0	0
Platelet ($x10^7$/ml)	0	0	0	0	0
BUN (mg/dl)	0	0	0	0	0
Creatinine (mg/dl)	0	0	0	0	0
Uric acid (mg/dl)	0	0	0	1 (3)	0
SGOT (mg/dl)	0	0	1 (43)	0	2 (49, 49)
SGPT (mg/dl)	0	0	0	0	2 (45, 47)
Triglyceride (mg/dl)	0	0	0	0	0
Cholesterol (mg/dl)	0	0	0	1 (255)	0
HDL (mg/dl)	0	0	0	0	0
LDL (mg/dl)	0	0	0	1 (172)	0
Total/HDL	0	0	0	0	0
Fasting Blood Sugar (mg/dl)	0	0	0	0	0

Discussion

Nutri-PEITC Jelly has been develop for potential use as chemoprevention and supportive care with anti-cancer effects for cancer patients. Previous studies by our group have reported a very high lethal dose 50 (LD50 more than 15,000 mg/kg) in acute toxicity test. Moreover, sub-acute toxicity analysis showed no toxic effects in rats taking 15,000 mg/kg Nutri-PEITC Jelly for 28 days and 14 days after finished taking the Nutri-PEITC Jelly (unpublished results). The pharmacokinetic study in Thai healthy subjects taking Nutri-PEITC Jelly with 40 mg PEITC per day for 5 days revealed no serious adverse effects[21]. Moreover, the study showed that PEITC in Nutri-PEITC Jelly was eliminated quickly with 2 hours half-life and 1.003 accumulation index[21], suggestive a very low accumulative effects. This study was the first to determine safety profile of Nutri-PEITC Jelly in healthy subjects after long period consumption. In accordance to previous studies, we reported that Nutri-PEITC Jelly was safe for 35-day consumption with mild adverse effects.

Other studies evaluating safety of isothiocyanate (ITC) in various forms have been reported such as ITC in broccoli, watercress and other cruciferous vegetables,

and PEITC dissolved in olive oil[28-30]. The results from those studies indicated that ITC could be toxic at high dose. However, when used at optimal concentration, no harmful effects were observed. Moreover, PEITC appears to have selective cytotoxicity towards cancer cells more than normal cells[12]. The pharmacokinetics study showed that PEITC in Nutri-PEITC Jelly formulation was more rapidly absorbed than that in oil which could be due to the ingredient and formulation of Nutri-PEITC Jelly[21]. Nevertheless, the safety profile of PEITC in all formulations was quite similar.

To our knowledge, our study was the first to evaluate effects of PEITC in Nutri-Jelly in human for a long period intake (5 weeks). Previously, only three repeated dosage studies of PEITC intake in human were done and the time of PEITC consumption was only 5 days, including 2 studies of 40 mg PEITC in olive oil per day and one study of 40 mg PEITC in Nutri-PEITC jelly per day[21, 31,32]. All three studies reported mild adverse events, consisting of dry mouth, taste alteration, stomachache, belching, flatulence, diarrhea, and pruritus. No hematologic abnormality was noted in one study[21] while the other two studies did not investigate the effects in this aspect[31,32]. The adverse events reported could be due to PEITC itself or non-specific. Nevertheless, they were mild and transient. Our current 7-week-study revealed a 16% incidence of oral discomfort, and abdominal bloating. PEITC is a member of isothiocyanates, which have been known to have pungency and tingling effects[33]. Therefore, the oral discomfort symptom is likely derived from PEITC. For gastrointestinal symptoms like abdominal bloating, milk is likely the major contributor since it is the major constituent in the Nutri-Jelly. Gastrointestinal disturbances such as abdominal pain and bloating are common symptoms when consuming milk especially when lactose is not fully digested[34]. Although Nutri-Jelly formulation contains lactose-hydrolyzed milk (low-lactose milk), the milk bloating symptoms can still occur. Consistently, a previous clinical study demonstrated that the abdominal bloating after consuming low-lactose were just reduced but did not completely disappear[35]. Another study also reported no significant difference in bloating symptoms between the full-lactose and low lactose milk if the milk consumption is less than 240 mL per day[36].

Other long-term studies related to PEITC that have been performed were in a form of cruciferous vegetable consumption. Watercress is one of the major source of PEITC. Ingestion of 56.8 grams watercress can release up to 12 mg PEITC[37]. A study in healthy participants who consumed 85 grams of raw watercress (approximate 18

mg PEITC) daily for 8 weeks showed no significant changes in LDL, HDL, and total cholesterol. Moreover, 10% reduction in plasma triacylglycerol concentration was reported[38].

In addition, Shapiro T *et al*. studied effects of aqueous extracts of broccoli sprouts containing controlled amount of isothiocyanates (ITC). The subjects were asked to consume broccoli sprout aqueous extracts equivalent to 75 µmol PEITC (12.2 mg) per day for 7 days. Consistent with our study, no evidence of systemic, clinically significant adverse effects were reported[39]. Another study showed that taking 400 grams per day Brussels sprouts for 18 days reduced warfarin efficacy[40]. Nevertheless, the amount consumed was very high and the potential mechanism for interference with warfarin function was most likely due to the high amount of vitamin K from Brussels sprout, not ITC[30].

Our data supported the safety of Nutri-PEITC Jelly in healthy volunteers. However, the clinical safety and efficacy of Nutri-PEITC Jelly are yet to be determined. Inhibition of CYP450 was shown to be an important mechanism of PEITC to reduce carcinogen and prevent cancer [1,41]. Since several anti-cancer drugs are metabolized by CYPs, future studies of PEITC in cancer patients must consider this possible drug interaction. A previous *in vivo* study demonstrated that consuming 0.1% PEITC in diet (approximately 80 mg/kg body weight) for 14 days resulted in urinary cell injury, which may contribute to an early event of urinary bladder carcinogenesis[42]. Another long-term study also showed that consuming 0.1% PEITC in the diet (approximately 80 mg/kg body weight/day) for 32 weeks promoted bladder carcinogenesis in rats pretreated with initiator carcinogen diethylnitrosamine (DEN) and N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)[43]. A recent review concluded that the carcinogenic potential of PEITC occurs post-initiation phase, i.e. the tumor must be pre-initiated by the other carcinogen, and PEITC acts as a promoter[44]. Interestingly, the human equivalent dose of the 80 mg PEITC/kg body weight/day in the rat is 800 mg/day for a person weighed 60 kg. Such an amount cannot be achieved from the regular consumption of vegetables since 30 g of fresh watercress contains only 7.6 mg of PEITC[44,45]. Nevertheless, if a high dose of PEITC was administered additionally, there is still a possible risk of developing bladder cancer, especially in the high-risk group with possible initiated carcinogens such as heavy smokers. Considering Nutri-PEITC Jelly, a box of 200 g contains 20 mg PEITC. Therefore, a person will need to consume as high as 40 boxes of 200 g Nutri-PEITC Jelly to reach the carcinogenic dose of PEITC, which is

nearly impossible. This simulated scenario suggests a safety window of Nutri-PEITC jelly. Nevertheless, to ensure maximum safety, cautions still should be made when using Nutri-PEITC Jelly in cancer-prone subjects. Combining dose of the product with individual existing exposure to PEITC from vegetable consumption should be taken into consideration to avoid possible toxicity.

The limitation of our study was that our subjects were not on diet restriction. This is because we would like to imitate real-world use condition. Nevertheless, medication use and alcohol consumption were recorded as they were involved in PEITC metabolism. Moreover, we did not measure serum levels of PEITC in our subject. However, frequent follow-up was done to ensure good compliance and very high compliance rate was received.

All these findings including ours, support the notion that Nutri-PEITC Jelly demonstrated acceptable safety profile. The adverse events reported were mild and only occurred in a small number of participants.

Conclusions

Our results demonstrate no significant adverse events and acceptable safety profile for 35-day consumption of Nutri-PEITC Jelly in healthy subjects. The knowledge gained from this study supports further development of Nutri-PEITC Jelly as a potential supportive care for cancer patients. Future safety and efficacy studies in cancer patients are warranted.

Ethical Approval

The research protocol was approved by the Ethics Committee of the Faculty of Dentistry, Srinakharinwirot University (protocol review no. SWU 5/2557). Granting organization was the Dental Innovation Foundation under Royal Patronage., Thailand

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Conflicts of interest

Dr. Lam-ubol and Dr. Trachootham received a research grant from the Dental Innovation Foundation under Royal Patronage. Other conflicts of interest: none.

Abbreviation

β-phenylethyl isothiocyanate (PEITC), cytochrome P (CYP), red blood cell counts (RBC), white blood cell counts (WBC), hematocrit (Hct), fasting blood sugar (FBS), blood urea nitrogen (BUN), high-density lipoprotein (HDL), how-density lipoprotein (LDL), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT)

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