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# Effects of Bojungikkitang (a Polyherbal Formula), on Gefitinib Pharmacokinetics in Rats

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ABSTRACT

Gefitinib is mainly used for treatment of non-small cell lung cancers and breast cancers, but many researcher have been interested in the combination therapies due to gefitinib-related toxicities. Bojungikkitang (BJIKT) is a traditional Korean herbal medicine for various tonic effects in patients with poor gastrointestinal functions and conditions debilitated from chronic diseases, which suggests possibility to improve cachexia in cancer patients or the immune system as an adjunctive therapy. Therefore, the pharmacokinetic interactions between gefitinib and BJIKT were examined as a first screening for the combination therapy. One batch of 10 rats received single oral co-administration of gefitinib with BJIKT (combination) or with distilled water (control). Another batch of 10 rats received repeated oral administration of the combination for 9 days after pretreatments with BJIKT for 7 days or control for 9 days after pretreatments with distilled water for 7 days. In the single and repeated co-administration, the gefitinib and BJIKT were used at doses of 50 and 100 mg $kg^{-1}$, respectively and the co-administration with BJIKT or distilled water was performed within 5 min after gefitinib. The plasma samples were collected time-dependently after the single administration and the initial and last treatment of the repeated administration. The analyzed pharmacokinetic parameters included peak concentration ($C_{max}$), time to reach the $C_{max}$, area under the plasma concentration-time curve, half-life and mean residence time to infinity. In the single administration, the gefitinib kinetic curves of plasma concentration were not different between the both of combination and control. There were no differences in the pharmacokinetic parameters between the both. It suggests little interactions between gefitinib and BJIKT. In addition, there were no interactions between gefitinib and BJIKT in the single co-administration after pretreatments for 7 days and even after the repeated co-administration for 9 days. This study provides basic information for the combination therapy of gefitinib with BJIKT.

**Key words:** Gefitinib, Bojungikkitang, pharmacokinetics, interactions, herbal products

## INTRODUCTION

Gefitinib (IRESSA™) is an oral inhibitor of Epidermal Growth Factor Receptor (EGFR) tyrosine kinase that plays a key role inactivating the tumor cell growth and survival (Wells, 1999; Baselga and Averbuch, 2000). Since, the EGFR is over expressed in the certain cell types of human carcinomas in the lung, breast and ovary, the gefitinib is mainly used for

Table 1: Composition of herbs for Bojungikkitang aqueous extracts

| Herbs | Scientific names | Amounts (g) |
|---|---|---|
| *Astragali radix* | *Astragalus membranaceus* Bunge | 1.000 |
| *Atractylodis rhizoma* | *Atracty lodeslancea* D.C | 1.000 |
| *Ginseng radix alba* | *Panax ginseng* C.A. Meyer | 1.000 |
| *Angelicae gigantis radix* | *Angelica gigas* N. | 0.750 |
| *Bupleuri radix* | *Bupleurum falcatum* L. | 0.500 |
| *Zizyphi fructus* | *Zizyphus jujuba* var. *Inermis* (Bunge) Rehder | 0.500 |
| *Citri unshii pericarpium* | *Citrus unshiu* S. Marcov. | 0.500 |
| *Glycyrrhizae rhizoma* | *Glycyrrhiz auralensis* Fisch | 0.375 |
| *Cimicifugae rhizoma* | *Cimici fugaheraclei folia* Kom. | 0.250 |
| *Zingiberis rhizoma siccus* | *Zingiber officinale* Roscoe | 0.125 |

Bojungikkitang (Jeil Pharm. Co., Seoul, Korea) is composed of 10 kinds of herbs at indicated amounts

treatment of non-small cell lung cancers and cancers in the breast and ovary as a selective antineoplastic agent (Costanzo *et al*., 2011; Murphy and Stordal, 2011). However, some adverse effects have been reported to use the gefitinib. The most common adverse effects are cutaneous reactions like rash and exfoliative or purpuric eruptions (Becuwe *et al*., 2007; Blume and Miller, 2007; Costanzo *et al*., 2011) and others include diarrhea, nausea, vomiting, anorexia and alveolar damage (Inoue *et al*., 2003; Van Zandwijk, 2003; Costanzo *et al*., 2011). In addition, the adverse effects have induced potential hazard for the fetus or pregnancy loss and the gefitinib-related deaths (Meyer zu Schwabedissen *et al*., 2006), suggesting that the clinical use of gefitinib needs careful cautions. There here have been some trials for the combination therapy of gefitinib with other drugs to reduce the adverse effects and achieve the synergic effects (Cascone *et al*., 2007). For the combination therapies, various pharmacokinetic interactions have been evaluated between gefitinib and drug transporters, CYP enzyme inhibitor or inducers and acid-reducing drugs including $H_2$-receptor antagonists and proton pump inhibitors (Peters *et al*., 2014), because the gefitinib is metabolized principally by a substrate of CYP3A4, the efficacy of gefitinib can be reduced in combination with CYP3A4 inducers (phenytoin, carbamazepine, rifampicin, barbiturates etc.), while potential toxicities can be enhanced with CYP3A4 inhibitors (azole antifungals, protease inhibitors, clarithromycin, telithromycin etc.). In addition, the gefitinib efficacy can be reduced in combination with $H_2$-receptor antagonists (ranitidine) or proton pump inhibitors (omeprazole) (Peters *et al*., 2014). However, the gefitinib has no pharmacokinetic interaction with cediranib, inhibitor of vascular endothelial growth factor receptor, which shows the enhanced anti-tumor activity in patients (Van Cruijsen *et al*., 2010).

Bojungikkitang (BJIKT; Bu-Zong-Yi-Qi-Tang in Chinese, Hochuekkito in Japanese) is a famous traditional Korean herbal medicine consisted of 10 kinds of herbs (Table 1), which is widely prescribed for treatments in weak patients with poor gastrointestinal functions and chronic diseases possessing symptoms, such as loss of appetite, mild fever, night sweat, palpitation, fear, restlessness, weak feeble voice, slurred speech and disturbance of vision (Scheid *et al*., 2009; Kiyohara *et al*., 2011). The various tonic effects have shown therapeutic benefits for the chronic fatigue in cancer patients (Jeong *et al*., 2010) and cachexia in mice cancer model (Wang *et al*., 2004; Yae *et al*., 2012). The BJIKT also has supportive effects on treatments of leukocytopenia in mice with anti-cancer agents (Kaneko *et al*., 1999) or atopic dermatitis (Kobayashi *et al*., 2010) and activation in the immune system (Kiyohara *et al*., 2011). It suggests that BJIKT can be useful in patients treated with gefitinib as an adjunctive therapy. Therefore, the pharmacokinetic analyses were examined between gefitinib and BJIKT for the combination therapy.

## MATERIALS AND METHODS

**Animals and husbandry:** Male Sprague-Dawley rats (6-wk old) were obtained from Japan SLC, Inc. (Shizuoka, Japan). The rats were housed five per polycarbonate cage (421×290×190 mm) in a room controlled at a temperature (20-25ºC) and humidity (40-45%) with 12 h light dark$^{-1}$ cycle. They were allowed free access to a commercial standard diet and water. All procedures were conducted with approval of the Institutional Animal Care and Use Committee at Daegu Haany University (Gyeongsan, Korea).

**Drugs and treatments:** Gefitinib (Iressa$^{TM}$) and BJIKT were purchased from Hangzhou Tacon Co., Ltd (Hangzhou, China) and Jeil Pharm. Co. (Seoul, Korea), respectively. They were stored at 4°C in dark until use. After 8 days acclimation, a total of 20 rats were allocated into 2 studies as indicated below; [Study I] single co-administration of gefitinib with BJIKT(combination) or gefitinib with distilled water (control) and [Study II] repeated co-administration of combination for 9 days after pre-treatments with BJIKT for 7 days or control for 9 days after pre-treatments with distilled water for 7 days. The BJIKT or distilled water was orally co-administered within 5 min after gefitinib. The gefitinib and BJIKT were used at doses of 50 and 100 mg kg$^{-1}$, respectively, based on the toxicity and pharmacodynamics (Culy and Faulds, 2002). Body weight was measured daily at every treatments.

**Blood collections:** All procedures for the pharmacokinetic analyses of gefitinib were performed, as described previously with some modification (Kang *et al*., 2014; Kim *et al*., 2015). After mild anesthesia under diethyl ether (Duksan Pure Chemical, Seoul, Korea), blood samples of 0.5 mL were collected into 50 IU heparinized tubes via the retro-orbital plexus at 0.5 h prior to the treatments and 1, 2, 3, 4, 6, 8 and 24 h post-treatments. The samples were immediately centrifuged at 11, 400 rpm for 10 min and the supernatants were stored at -70°C in the plasma aliquots until pharmacokinetic analyses.

**Sample preparation and calibrations:** Primary stock solution of gefitinib (Sigma, MO, USA)was prepared at 1.0 mg mL$^{-1}$ in acetonitrile and further diluted for working standard solutions. Carbamazepine (Sigma, MO, USA) was prepared at 500 ng mL$^{-1}$ in acetonitrile for Internal Standard (IS) working solution. For the calibration of gefitinib, the dose-dependent

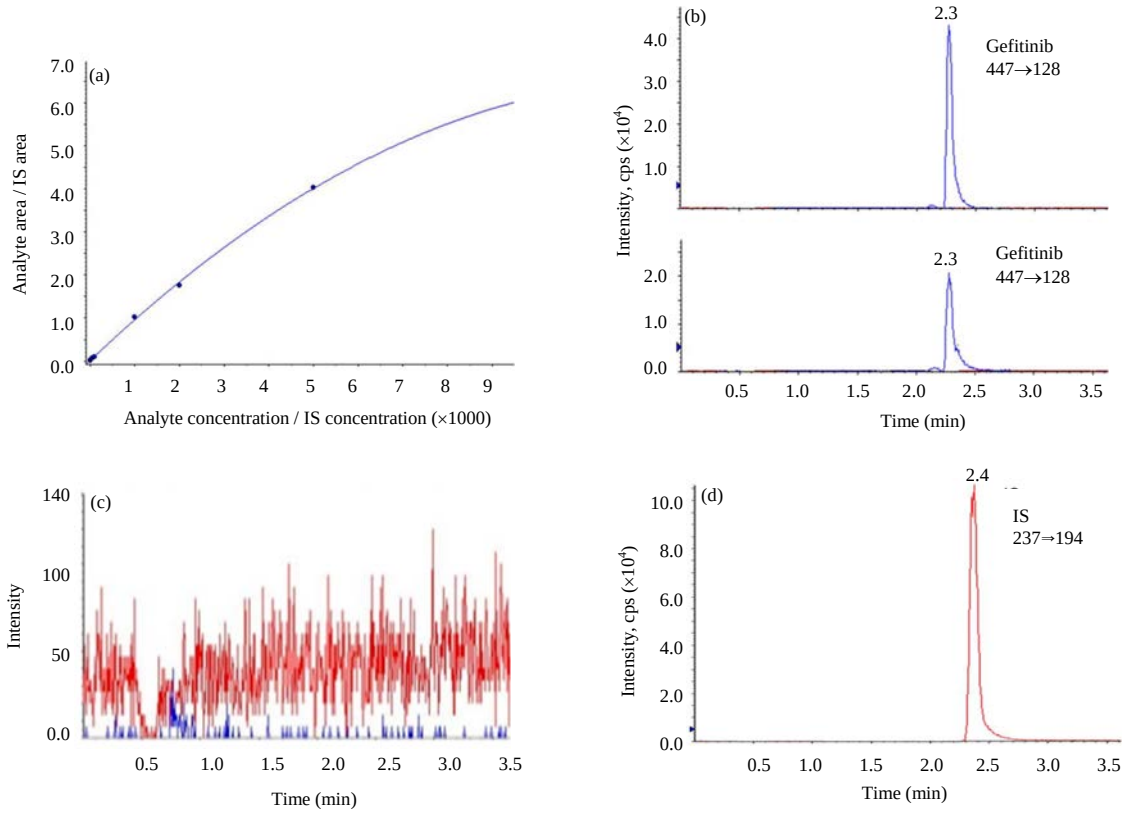


Fig. 1(a-d): Mass chromatograms and profiles for gefitinib. The plasma samples were analyzed by LC-MS/MS with carbamazepine as an Internal Standard (IS), (a) Plasma calibration curve of gefitinib at 1 ng $mL^{-1}$-10 μg $mL^{-1}$ ($r^2$>0.999). (b) Mass chromatograms of blank plasma spiked with gefitinib at 1 μg $mL^{-1}$ (upper) or the plasma sample (lower) and (c-d) Mass chromatograms of double blank and blank plasma spiked with carbamazepine at 500 ng $mL^{-1}$

working standard solution of volume of 100 μL was mixed with each 100 μL of blank plasma and IS working solution in acetonitrile of 100 μL. The plasma samples of 100 μL were mixed with 100 μL is working solution in acetonitrile of 200 μL for the pharmacokinetic analyses of gefitinib. The mixtures were mixed with vortex-mixing and centrifuged at 9,700×g for 10 min at 4°C. The clear supernatants of 5 μL were transferred to injection vials for the LC-MS/MS system.

**LC-MS/MS conditions**: The concentration of gefitinib was measured by LC-MS/MS using an API 2000 system (Applied Biosystems, Foster City, CA, USA) with an Agilent 1100 Series HPLC (Agilent Technologies, Santa Clara, CA, USA). Analytes were separated using Waters Xterra MS $C_{18}$ columns (2.1×50 mm, 3.5 μm) (Waters Corp, Milford, MA, USA) at column oven of 30°C. The gradient mobile phase was composed of 2-98% acetonitrile in distilled water containing 0.1% formic acid and it was delivered at 0.35 mL $min^{-1}$. The Turboion Spray was introduced in the positive ion mode at 400°C and 5.0 Kv. Nitrogen was used as nebulizer, curtain and collision gas with set of 12, 6 and 8 psi, respectively. The mass transitions used to quantify gefitinib and IS were m/z 447→128 (retention time: 2.3 min) and 237→194 (retention time: 2.4 min), respectively. Calibration curves of gefitinib were linear over the ranges studied with $r^2$>0.999 and the lower limit of quantification was 1 ng $mL^{-1}$. The coefficient of variation for the assay precision was less than 15% and the accuracy was 89-113%. The average extraction recoveries were more than 80% in the plasma. The plasma calibration for gefitinib and MS profiles for gefitinib and IS, scanned by differention pairs are shown in Fig. 1. The analytical data were processed by the Analyst version 1.4.2 software (Applied Biosystems).

**Pharmacokinetic analyses:** The plasma concentration of gefitinib was analyzed using a non-compartmental method on commercial pharmacokinetics data analyzer programs (PK solutions 2.0; Summit, CO, USA) (Gibaldi and Perrier, 1982; Bailer, 1988). The elimination rate constant ($K_{el}$) was calculated by log-linear regression of gefitinib concentration during elimination phase and terminal half-life ($t_{1/2}$) was calculated by 0.693/$K_{el}$. Peak concentration of gefitinib ($C_{max}$) and time to reach the $C_{max}$ ($T_{max}$) were obtained by visual inspection of the data in plasma concentration-time curve.

Area Under the Concentration-time curve ($AUC_{0-t}$) from time zero to the time of the last measured concentration ($C_{last}$) was calculated using the linear trapezoidal rule (Chiou, 1978). The AUC from time zero to infinity ($AUC_{0-inf}$) was obtained by adding $AUC_{0-t}$ and the extrapolated area was determined by $C_{last}/K_{el}$. The mean residence time zero to infinity ($MRT_{inf}$) was calculated by dividing the first moment of AUC by $AUC_{0-inf}$.

**Statistical analyses:** All data are represented as Mean±SD. Variance of homogeneity was examined using the Levene test. If the Levene test indicated no significances, data were analyzed by independent t-test. If the Levene test indicated significances, data were analyzed by Mann-Whitney U-test. The statistical significance was considered at $p<0.05$.

## RESULTS

**Changes on gefitinib pharmacokinetics in single co-administration of gefitinib with BJIKT (Study I):** In the single administration, no meaningful changes were observed in the plasma concentration of gefitinib between the both groups of combination and control (Fig. 2). There were no significant differences in the pharmacokinetic parameters between the both groups (Table 2).

**Changes on gefitinib pharmacokinetics in repeated co-administration of gefitinib with BJIKT after pretreatments with BJIKT (Study II):** In the repeated administration, there were no differences in body weights between the both groups of combination and control (data not shown).

In the initial treatments of the repeated administration after the pre-treatments for 7 days, no significant changes were observed in the plasma concentration of gefitinib between the both groups of combination and control (Fig. 3a). In addition, there were no significant differences in the pharmacokinetic parameters between the both groups (Table 3).

Similarly, in the last treatments of the repeated administration for 9 days, no changes were observed in the plasma concentration of gefitinib between the both groups (Fig. 3b). There were no differences in the pharmacokinetic parameters between the both groups (Table 4).

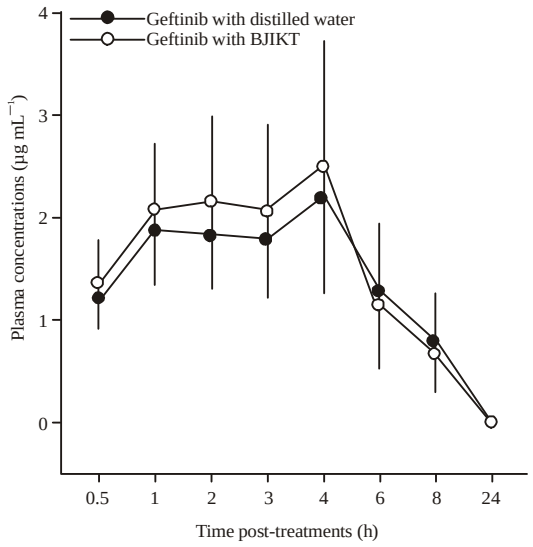


Fig. 2: Effects of single co-administration of gefitinib with Bojungikkitang on plasma concentration of gefitinib. The pharmacokinetic graph indicates plasma concentration of gefitinib at the indicated times after the co-administration of gefitinib with Bojungikkitang for combination or gefitinib with distilled water for control. Values were expressed as Mean±SD of 5 rats per group

## DISCUSSION

Clinical use of gefitinib can be considered as the first-line option for treatment in non-small cell lung cancers, but many studies have been interested in the combination therapy due to the gefitinib related adverse effects. The gefitinib is known to have interactions with CYP enzyme inhibitors or inducers and acid-reducing drugs including $H_2$-receptor antagonists and proton pump inhibitors (Peters *et al*., 2014). The drug interactions can cause increases of toxicities or reduction of efficacy, depending on the changes of pharmacokinetic absorption, metabolism or excretion by the co-administered

Table 2: Effects of single co-administration of gefitinib with Bojungikkitang on gefitinib pharmacokinetics

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (μg $mL^{-1}$) | 2.16±0.76 | 2.54±1.18 |
| $T_{max}$ (h) | 3.40±1.34 | 3.00±1.41 |
| $AUC_{0-t}$ (μg h $mL^{-1}$) | 14.60±9.45 | 15.16±9.87 |
| $AUC_{0-inf}$ (μg h $mL^{-1}$) | 16.39±9.31 | 16.46±9.66 |
| $t_{1/2}$ (h) | 2.59±0.76 | 2.30±0.73 |
| $MRT_{inf}$ (h) | 5.05±0.90 | 4.35±0.75 |

Plasma samples of rats used in Fig. 2 were analyzed for the pharmacokinetic parameters. Values are expressed as Mean±SD in 5 rats

Table 3: Effects of pretreatments with Bojungikkitang on gefitinib pharmacokinetics

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (μg $mL^{-1}$) | 3.01±0.48 | 3.41±0.15 |
| $T_{max}$ (h) | 4.00±0.00 | 4.00±0.00 |
| $AUC_{0-t}$ (μg h $mL^{-1}$) | 15.35±2.24 | 15.94±1.22 |
| $AUC_{0-inf}$ (μg h $mL^{-1}$) | 20.17±4.61 | 19.19±2.00 |
| $t_{1/2}$ (h) | 2.82±0.92 | 2.25±0.27 |
| $MRT_{inf}$ (h) | 5.94±1.36 | 5.20±0.29 |

Plasma samples of rats used in Fig. 3a were analyzed for the pharmacokinetic parameters. Values are expressed as Mean±SD in 5 rats

Table 4: Effects of repeated co-administration of gefitinib with Bojungikkitangon gefitinib pharmacokinetics

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (μg $mL^{-1}$) | 3.12±0.77 | 2.98±0.25 |
| $T_{max}$ (h) | 4.00±0.00 | 3.60±0.89 |
| $AUC_{0-t}$ (μg h $mL^{-1}$) | 13.53±2.78 | 14.73±1.98 |
| $AUC_{0-inf}$ (μg h $mL^{-1}$) | 16.88±4.14 | 17.87±2.77 |
| $t_{1/2}$ (h) | 2.38±0.88 | 2.34±0.33 |
| $MRT_{inf}$ (h) | 5.71±1.04 | 5.21±0.44 |

Plasma samples of rats used in Fig. 3b were analyzed for the pharmacokinetic parameters. Values are expressed as Mean±SD in 5 rats

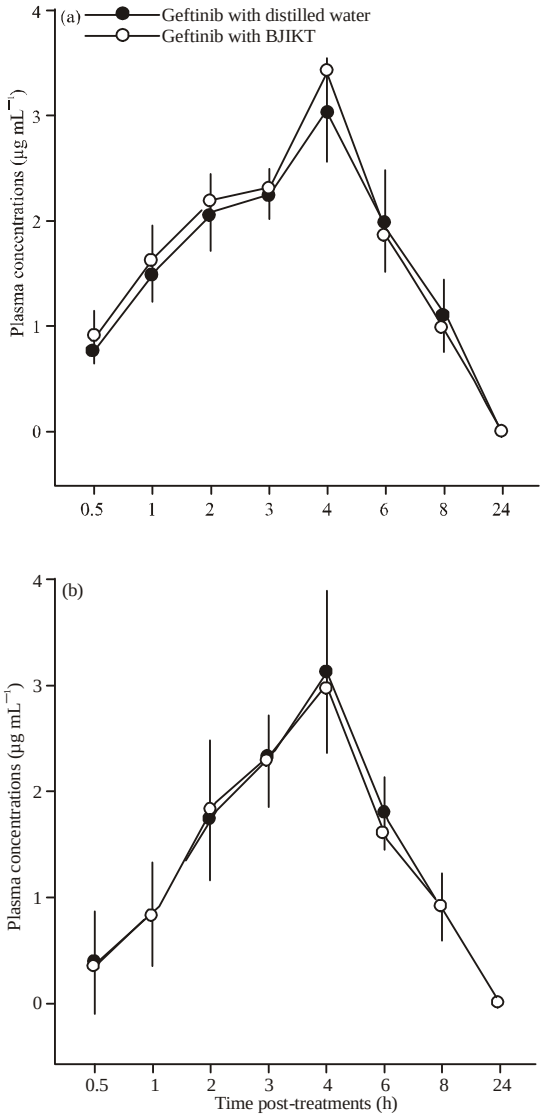


Fig. 3: Effects of pretreatments with Bojungikkitang (BJIKT) or repeated co-administration of gefitinib with BJIKT on plasma concentration of gefitinib. Rats were pretreated with Bojungikkitang (BJIKT) for 7 days, followed by repeated combination of gefitinib with BJIKT for 9 days or pretreated with distilled water for 7 days, followed by repeated control of gefitinib with distilled water for 9 days. The graphs indicate the plasma concentration of gefitinib after (a) the initial and (b) last treatments of the repeated co-administration. Values were expressed as Mean±SD of 5 rats per group

drugs. Currently, there have been reported to have little pharmacokinetic interactions between gefitinib and cediranib (Van Cruijsen *et al*., 2010) or cisplatin (Giaccone *et al*., 2004), which has shown the synergistic and additive effects in clinical responses. In addition, there have been also reported to have enhanced anti-tumor effects in combination of gefitinib with carboplatin, oxaliplatin, paclitaxel, docetaxel, doxorubicin, etoposide, topotecan and raltitrexed (Ciardiello *et al*., 2000). However, the interaction of gefitinib with carboplatin or paclitaxel has potential risk of hematological disorders and other combinations need further safety investigations (Hammond, 2003).

There are a few studies on pharmacokinetic interactions between gefitinib and herbal products. The most of pharmacokinetic studies have shown significant interactions between gefitinib and warfarin (Arai *et al*., 2009), an herbal medicines with ginseng, mushrooms and selenium (Hwang *et al*., 2008) and Marsdeniatenacissima extract (Han *et al*., 2014), which result in reduced anti-tumor effects of gefitinib or reduced efficacy of combined drugs. Here, co-administration with BJIKT appeared to influence little in the oral bioavailability of gefitinib, although BJIKT include ginseng and other 9 herbs. The results showed little interactions in single co-administration of gefitinib and BJIKT with or without pretreatments with BJIKT for 7 days. Furthermore, the interaction was also observed little even after the repeated co-administration for 9 days. It suggests that BJIKT can be co-administered with gefitinib as an adjunctive medicine.

BJIKT has shown improvement of cancer-related fatigue and quality of life in patients with chronic diseases. Among the ingredients composing the BJIKT, Astragali radix has immuno-modulatory effects (Cai *et al*., 2006; Wei *et al*., 2006) and ameliorates anorexia in cancer (Lee and Lee, 2010). Ginseng is known to have anti-fatigue, anti-stress and anti-oxidative effects (Bruera *et al*., 2006) and Glycyrrhizae radix has preventive effects on endometrial carcinogenesis (Niwa *et al*., 1999). The exact mechanisms regarding how the individual ingredients affects in the anti-tumor activities of BJIKT are unclear, but the individual herbs may be adjusted for additional synergistic effects under monitoring the pharmacokinetic interactions in combination with gefitinib. Further clinical studies may provide detailed information for the proper dose regimen that generates enhanced combination effects. Overall, these suggest possibility to use a BJIKT in combination with gefitinib as a novel combination therapy.

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