Study of Pharmacodynamic and Pharmacokinetic Interaction of Bojungikki-Tang with Aspirin in Healthy Subjects and Ischemic Stroke Patients

Jung-Hwa Yoo, Sung-Vin Yim, and Byung-Cheol Lee

Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, 23 Kyungheedae-ro, Dongdaemun, Seoul 02447, Republic of Korea

Department of Pharmacology, School of Medicine, Kyung Hee University, 23 Kyungheedae-ro, Dongdaemun, Seoul 02447, Republic of Korea

Correspondence should be addressed to Byung-Cheol Lee; hydrolee@khu.ac.kr

Received 26 October 2017; Accepted 24 December 2017; Published 23 January 2018

Background. Bojungikki-tang (BJIKT) is a widely used traditional herbal formula in China, Japan, and Korea. There have been reports that several herbs among BJIKT have interactions with antiplatelet drugs, such as aspirin. This study aimed to assess whether BJIKT interacts with aspirin in terms of pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects and ischemic stroke patients.

Methods. The phase I interaction trial was a randomized, open-label, crossover study of 10 healthy male subjects, and the phase III interaction trial was a randomized, placebo-controlled, parallel study of 43 ischemic stroke patients. Each participant randomly received aspirin + BJIKT or aspirin + placebo. For PK analysis, plasma acetyl salicylic acid (ASA) and salicylic acid (SA) were evaluated, and, for PD analysis, platelet aggregation and plasma thromboxane B₂ (TxB₂) were measured.

Results. In the PK parameters, mean area under curve, maximum concentration, and peak concentration time of ASA and SA were not different between the two groups in healthy subjects and ischemic stroke patients. In the PD profiles, TxB₂ concentrations and platelet aggregation were not affected by coadministration of BJIKT in healthy subjects and ischemic stroke patients. These results suggest that coadministration of BJIKT with aspirin may not result in herb-drug interaction.

Conclusions. The results of this study suggest that coadministration of BJIKT with aspirin may not result in herb-drug interaction.
Table 1: Baseline characteristics of healthy subjects and ischemic stroke patients.

|                                | Healthy subjects (n = 10) | Aspirin + placebo (n = 21) | Ischemic stroke | Aspirin + BJIKT (n = 22) | P |
|--------------------------------|---------------------------|---------------------------|-----------------|--------------------------|---|
| Age (y)                        | 28.7 ± 4.2                | 60.0 ± 10.9               | 64.7 ± 7.1      | NS                       |
| Male (n, %)                    | 10 (100)                  | 13 (61.9)                 | 14 (63.6)       | NS                       |
| BMI (kg/m²)                    | 23.7 ± 1.7                | 24.7 ± 3.1                | 24.1 ± 1.7      | NS                       |
| Heart disease (n, %)           | 0                         | 3 (14.2)                  | 7 (31.8)        | NS                       |
| HBP (n, %)                     | 0                         | 13 (61.9)                 | 14 (63.6)       | NS                       |
| Diabetes (n, %)                | 0                         | 6 (28.5)                  | 6 (27.2)        | NS                       |
| Dyslipidemia (n, %)            | 0                         | 10 (47.6)                 | 9 (40.9)        | NS                       |
| Smoking (n, %)                 | 0                         | 2 (9.5)                   | 2 (9.1)         | NS                       |
| Alcohol (n, %)                 | 0                         | 7 (33.3)                  | 8 (36.3)        | NS                       |

BJIKT: Bojungikki-tang, BMI: body mass index, and HBP: high blood pressure.

and pharmacodynamics (PD) in healthy individuals as well as in ischemic stroke patients.

2. Materials and Methods

2.1. Subjects. The phase I study population consisted of 10 healthy adult male volunteers. The mean age was 25.4 ± 3.4 years (20–33 years). The mean body weight was 70.9 ± 10.2 kg and the mean height was 175.5 ± 4.9 cm. Significant exclusion criteria for study included a history of allergy to aspirin or herbal medication; history of renal, hepatic, cardiovascular, gastrointestinal, or neurologic diseases that might significantly alter the absorption, distribution, metabolism, and excretion of the study drug; known hypersensitivity to the study drugs; acute disease within the past 28 days from the administration of a drug; participation in another clinical study within the past 60 days; receiving medications that induce or inhibit drug-metabolizing enzymes, such as barbiturates, within past 30 days; history of excessive drinking; illiteracy; or inability to be protected by parental rights.

The phase III study population was selected from 322 ischemic stroke patients over 40 years old (range 41–77 years) who were living in Korea. Prospective participants were screened at Kyung Hee University Medical Center from March 2010 to April 2011. Of these, 43 subjects participated in this study. The inclusion criteria included individuals taking aspirin for over 3 months with a previous diagnosis of ischemic stroke, defined as an acute focal or global neurological deficit lasting more than 24 hours without an apparent cause other than vascular origin, consecutively confirmed by magnetic resonance imaging (MRI) within 72 hours of the onset of symptoms. Patients with cerebral hemorrhage, cerebral venous thrombosis, or a brain tumor and those who met any of the phase I exclusion criteria were excluded. Of the 43 ischemic stroke patients enrolled in phase III, 39 subjects completed the study and were included in PK and immunogenicity analyses (17, aspirin + BJIKT; 22, aspirin + placebo). Four subjects from the aspirin + placebo group and 0 subjects in the aspirin + BJIKT group withdrew consent after receiving the study drug. The baseline demographic characteristics of subjects in each group were well balanced within the groups (Table 1).

Both phase I and phase III studies were approved by the institutional review board of Kyung Hee University Medical Center (phase I: KMC IRB 0917-03-A2; phase III: KOMC IRB 2009-15) and were also approved by Korean Food Drug Administration (KFDA) (phase I: 2010-135; phase III: 2009-1080). Written informed consent was obtained from each participant, and studies were conducted in accordance with the principles of the International Conference of Harmonization for Good Clinical Practice (ICH-GCP) and the ethical standards for human experimentation established in the Declaration of Helsinki. The study was registered with Clinical Research Information Service (CRIS): KCT0002049.

2.2. Study Drugs. We purchased the BJIKT extract granules that contain a mixture of spray-dried hot water extracts of 10 medicinal plants from Hanpoong Pharmacy & Foods Company (Seoul, Korea). The 10 medicinal plants are Astragali radix (16.7%), Atractylodis lanceae rhizoma (16.7%), Ginseng radix (16.7%), Angelicae rhizoma (12.5%), Bupleuri radix (8.3%), Zizyphi fructus (8.3%), Aurantii nobilis pericarpium (8.3%), Glycyrrhizae radix (6.3%), Cimicifugae rhizoma (4.2%), and Zingiberis rhizoma (2.0%). A voucher specimen (code number HX018) was deposited in herbarium in the department of herbal pharmacy, Kyung Hee Korean Medical Hospital.

Each herb in BJIKT was quality controlled from the places of origin to the final products. The active ingredients were also quality controlled by using high-performance liquid chromatography. According to the compilation of specification and test procedures of Hanpoong Pharmacy & Foods Company, BJIKT contains 52.0 mg of hesperidin (C_{27}H_{52}O_{15} in Citri Unshii Pericarpium), 5.4 mg of ginsenoside Rb_{1} (C_{34}H_{49}O_{17} in Ginseng radix), 50.0 mg of decursin (C_{19}H_{20}O_{5} in Angelicae Gigantis Radix), 6 mg of zingerol (C_{17}H_{26}O_{2} in Zingiberis Rhizoma), and 67.5 mg of glycyrrhizic acid (C_{42}H_{62}O_{16} in Glycyrrhizae Radix et Rhizoma) per pack.

And enteric-coated tablet aspirin (Aspirin Cardio™) 100 mg was donated from Bayer HealthCare Pharmaceuticals, Germany.
2.3. Protocol. The phase I interaction study was conducted in the Kyung Hee Clinical Research Institute, Kyung Hee Medical Center, Kyung Hee University (Seoul, Korea). It was a randomized, open-label, crossover study of 10 healthy male subjects. A day before the study, eligible subjects were hospitalized in the Kyung Hee Clinical Research Institute. After overnight fasting, each subject randomly received an oral administration of 3 packs of BJIKT or placebo (1 pack volume: 6.83 g) at 7 AM and additionally given the 2 capsules of Aspirin Cardio 100 mg (Bayer HealthCare Pharmaceuticals, Germany) at 8 AM with 240 mL tap water. For the pharmacokinetic analysis, blood acetyl salicylic acid and salicylic acid were measured 0, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, and 600 min after aspirin administration. For pharmacodynamic analysis, platelet aggregation was measured 0, 2, and 4 h, and plasma thromboxane B2 (TxB2) was measured 0, 5, 10, 20, 30, 45, and 60 min after aspirin administration. After 1 week wash-out period, administration of each group was exchanged, and all measurements were repeated in the same manner.

The phase III interaction study was conducted at Kyung Hee Korean Medical Hospital, Kyung Hee University (Seoul, Korea). It was a randomized, placebo-controlled, double-blinded, parallel study. Eligible ischemic stroke patients were randomly allocated to either BJIKT treatment or placebo, in addition to aspirin. After allocation, each subject randomly received oral administration of BJIKT or placebo 3 times a day (1 pack volume: 6.83 g) as well as 1 capsule of Aspirin Cardio 100 mg every morning for 2 weeks [15]. For PK analysis, blood ASA and SA were measured 2 hours after aspirin administration at 0, 1, and 2 weeks. For PD analysis, platelet aggregation and plasma TxB2 were measured 1 hour after aspirin administration at 0, 1, and 2 weeks. At every visit, all of the laboratory tests done at screening as well as basic exams (weight, height) were repeated. Blood samples were collected for participant safety and outcome assessment. Participants were asked about adverse events, and BJIKT packs and aspirin capsules were counted to assess compliance (Table 5).

2.4. Measurement of Acetyl Salicylic Acid and Salicylic Acid. Plasma concentration of acetyl salicylic acid (ASA) and salicylic acid (SA) which is the further metabolite of ASA was determined with liquid chromatography (UPLC, Waters Corp) tandem mass spectrometry (Qtrap 5500, AB scieix). The compounds were separated using reverse column (ACQUITY UPLC C18 Column, 1,7 μm, 2.1 × 50 mm) with an isotropic mobile phase consisting of acetonitrile and water (70: 30, v/v; with 0.1% formic acid) at flow rate 0.2 ml/min. Detection was performed using electrospray ionization (ESI) source in the negative ion mode at −4500 eV and 600°C. The operating conditions were optimized for each of the analytes and were determined as follows: nebulizing gas (Gas1), 60; heater gas (Gas2), 60; curtain gas, 30. Quantification was performed by multiple-reaction monitoring (MRM). The masses for ASA and SA were m/z 179 → 135 (with declustering potential −80, collision energy −16) and 136.8 → 93 (with declustering potential −140, collision energy −15.5). The internal standard of this study was simvastatin and the mass was m/z 434.6 → 367 (with declustering potential −60, collision energy −15). The lower limit of quantification (LLOQ) for ASA and SA was 5 ng/mL and 50 ng/mL, respectively.

Pharmacokinetic parameters for ASA and SA were determined including Cmax (maximum plasma concentration), Tmax (time point of maximum plasma concentration), and AUC0–∞ (area under the plasma concentration versus time curve from 0 h to infinity).

2.5. Measurement of Platelet Aggregation and Plasma Thromboxane B2 Level. Platelet aggregation experiments were performed using Chrono-Log model 700 two-channel whole Blood/Optical Lumi-Aggregometer (Chrono-Log Corporation). Platelet-rich plasma (PRP) was obtained from the citrated blood centrifugation (Beckman Allegra 6R) at 800 rpm for 10 min. Platelet-poor plasma (PPP) was obtained from PRP centrifugation (ependorf 5415R) at 13000 rpm for 10 min. Collagen (Chrono-Log Corporation) was used to induce the platelet aggregation. The change in absorbance was recorded until the response reached a plateau or for 5 min.

Plasma thromboxane B2 (TxB2) was measured using an enzyme immunoassay kit (Thromboxane B2 EIA Kit, Cayman Chemical, MI, USA). The standard curve was prepared as outlined in the manufacturer's instructions. The thawed test and control plasma samples were tested in duplicate.

2.6. Statistical Analysis. The study sample sizes were determined from variance estimates based on prior aspirin platelet aggregation PD data [15]. To evaluate clinically relevant interactions, we used the noninferiority approach with 90% test power and a two-sided alpha value of 0.05. Data were presented as the mean ± standard deviation. Baseline demographics and clinical variables in the phase III study were compared among treatment groups using a Student's t-test, chi-square test, or Fisher's exact test. The changes in PK or PD 1 and 2 weeks from baseline were compared between the BJIKT treatment group and the placebo group using a Student's t-test. All P values were two-tailed, and significance was set at P < 0.05. All statistical analyses were performed using the GraphPad Prism for Windows, Version 5.01 (GraphPad Software, Inc.).

3. Results

3.1. Pharmacokinetic Effects of Aspirin and Bojungikki-Tang Coadministration. In the phase I trial with healthy subject, the area under curve (AUC) of acetyl salicylic acid in placebo group was 60959.5 ± 14243.3 ng/ml, while in BJIKT group it was 53465.3 ± 6777.6 ng/ml. Mean ± SE peak plasma concentration (Cmax) value in the placebo was 440.8 ± 100.8 ng/ml, while in the BJIKT it was 418.2 ± 81.5 ng/ml. Time to peak concentration (Tmax) of salicylic acid in placebo was 312.0 ± 43.6 min, while in the BJIKT it was 312.0 ± 24.9 min. There were no significant differences between two groups in mean values of AUC, Cmax, and Tmax (Table 2, Figure 1). The plasma concentrations of salicylic acid at various time intervals have been plotted in Figure 1. When an Aspirin was administrated with BJIKT, the area under the curve (AUC) of salicylic acid in placebo
Table 2: Pharmacokinetic parameters among healthy subjects (phase I study).

|                  | Aspirin + placebo | Aspirin + BJIKT | P    | Aspirin + placebo | Aspirin + BJIKT | P    |
|------------------|-------------------|-----------------|------|-------------------|-----------------|------|
| AUC₀–last (ng/mL)| 60959.5 ± 14243.3 | 53465.3 ± 6777.6 | N.S. | 1704207.8 ± 276367.4 | 1986552.4 ± 252995.5 | NS   |
| Cₘₐₓ (ng/mL)    | 440.8 ± 100.8     | 418.2 ± 81.5    | N.S. | 6284.3 ± 1029.1    | 7550.8 ± 906.2   | NS   |
| Tₘₐₓ (min)      | 312.0 ± 43.6      | 312.0 ± 24.9    | N.S. | 414.0 ± 44.2       | 348.0 ± 21.5     | NS   |
| t₁/₂ (min)      | 68.4 ± 21.6       | 50.1 ± 10.7     | N.S. | 319.2 ± 118.6      | 252.0 ± 57.4     | NS   |

BJIKT: Bojungikki-tang, ASA: acetylsalicylic acid, SA: salicylic acid, AUC₀–last: area under the serum concentration-time curve from time 0 to 10 hours after aspirin administration, Cₘₐₓ: maximum plasma concentration, Tₘₐₓ: time point of maximum plasma concentration, and t₁/₂: terminal elimination half-life.

Figure 1: The pharmacokinetic profiles of healthy subjects (phase I study). Data are shown as mean and standard deviation of acetylsalicylic acid (a) and salicylic acid levels (b) in Bojungikki-tang (BJIKT) + aspirin and placebo + aspirin.

3.2. Pharmacodynamic Effects of Aspirin and Bojungikki-Tang Coadministration. In the phase I trial with healthy subject, when aspirin was administrated with a placebo, a 60.5% rapid decrease in mean plasma TxB₂ concentrations compared with baseline was detected at 5 min (P < 0.001). In the BJIKT group, a 62.2% decrease in mean plasma TxB₂ was also detected at 5 min (P < 0.001) (Table 3, Figure 2).
Table 4: Change in pharmacokinetic and pharmacodynamic profiles and blood tests among ischemic stroke patients (phase III study).

|                      | Aspirin + placebo | Aspirin + BJIKT | P     |
|----------------------|-------------------|-----------------|-------|
| **PK**               |                   |                 |       |
| ASA                  | 27.8 ± 17.4       | 19.1 ± 11.5     | −18.3 ± 14.1 | NS   |
| SA                   | 2953.7 ± 571.2    | 2298.6 ± 598.2  | −374.1 ± 506.3 | NS   |
| **PD**               |                   |                 |       |
| TxB₂ (pg/ml)         | 16.2 ± 3.4        | 21.1 ± 5.3      | −13.6 ± 3.6 | NS   |
| PLT agg (%)          | 74.8 ± 3.6        | 73.6 ± 2.5      | −1.1 ± 2.8  | NS   |
| **Blood chemistry**  |                   |                 |       |
| FBG (mg/dl)          | 117.9 ± 39.8      | 120.8 ± 48.7    | −9.2 ± 59.9 | NS   |
| T-chol (mg/dl)       | 171.0 ± 41.7      | 171.7 ± 38.5    | −5.1 ± 22.9 | NS   |
| TG (mg/dl)           | 153.7 ± 82.3      | 161.7 ± 69.9    | −5.3 ± 57.4 | NS   |
| Ca                   | 9.2 ± 0.3         | 9.1 ± 0.2       | 4.0 ± 18.1  | NS   |
| P                    | 3.1 ± 0.6         | 3.1 ± 0.5       | 0.08 ± 0.4  | NS   |
| Uric acid            | 5.5 ± 1.5         | 5.4 ± 1.6       | −0.3 ± 0.6  | NS   |
| **Blood count**      |                   |                 |       |
| WBC                  | 6.5 ± 1.0         | 6.8 ± 1.1       | −0.1 ± 0.5  | NS   |
| RBC                  | 4.7 ± 0.5         | 4.5 ± 0.5       | 0.0 ± 0.2   | NS   |
| Hgb                  | 14.1 ± 1.6        | 13.8 ± 1.5      | 0.1 ± 0.5   | NS   |
| Hct                  | 41.4 ± 4.4        | 40.6 ± 4.6      | 0.2 ± 1.9   | NS   |
| Platelet             | 277.1 ± 82.2      | 263.7 ± 69.9    | 9.9 ± 37.6  | NS   |

BJIKT: Bojungikki-tang, ASA: acetylsalicylic acid, SA: salicylic acid, TxB₂: thromboxane B₂, PLT agg: platelet aggregation, FBG: fasting blood glucose, T-chol: total cholesterol, TG: triglyceride, Ca: calcium, P: phosphorus, WBC: white blood cell, RBC: red blood cell, Hgb: hemoglobin, and Hct: hematocrit.

Table 5: Safety parameters among ischemic stroke patients (phase III study).

|                      | Aspirin + placebo | Aspirin + BJIKT | P     |
|----------------------|-------------------|-----------------|-------|
| **Liver function**   |                   |                 |       |
| AST                  | 24.7 ± 4.9        | 25.2 ± 5.4      | 2.0 ± 6.3 | NS   |
| ALT                  | 23.5 ± 11.7       | 21.4 ± 8.1      | 1.6 ± 6.2 | NS   |
| GGT                  | 29.6 ± 12.5       | 29.1 ± 16.2     | 0.1 ± 4.9 | NS   |
| T-bil                | 0.6 ± 0.2         | 0.6 ± 0.2       | 0.0 ± 0.1 | NS   |
| ALP                  | 78.1 ± 16.9       | 68.5 ± 15.8     | 0.8 ± 6.2 | NS   |
| Protein              | 7.6 ± 0.5         | 7.4 ± 0.4       | −0.0 ± 0.4 | NS   |
| Albumin              | 4.4 ± 0.1         | 4.3 ± 0.2       | −0.0 ± 0.1 | NS   |
| **Kidney function**  |                   |                 |       |
| BUN                  | 15.6 ± 2.5        | 16.6 ± 5.3      | −2.3 ± 4.7 | NS   |
| Cr                   | 0.7 ± 0.1         | 0.8 ± 0.4       | −0.0 ± 0.0 | NS   |
| **Adverse effects**  |                   |                 |       |
| Indigestion          | 1                 | 1               | NS     |
| Diarrhea             | 1                 | 0               | NS     |

BJIKT: Bojungikki-tang, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, T-bil: total bilirubin, ALP: alkaline phosphatase, and BUN: blood urea nitrogen.

A statistically significant decrease in plasma TxB₂ was not detected in either the BJIKT or placebo groups at baseline or various time intervals. The inhibition of platelet aggregation at various time intervals for the BJIKT or placebo groups combined with aspirin was analyzed. In the placebo group, platelet aggregation with 300 mg of aspirin was found to be 66.7 ± 14.7% at 4 h compared with 77.4 ± 5.4% at baseline (P < 0.001). In the BJIKT group, the platelet was decreased to 66.9 ± 14.9% at 4 h compared with 78.1 ± 5.4% at baseline (P < 0.001). However, the combination of aspirin with either BJIKT or a placebo did not potentiate the inhibition of collagen-induced platelet aggregation (Table 3, Figure 2).

In the phase III trial with ischemic stroke patients, the effects of the combination of aspirin with either BJIKT or
placebo on plasma TxB₂ concentrations are shown in Table 4. When aspirin was administrated with a placebo, the mean plasma TxB₂ concentrations decreased $-13.9 \pm 2.5$ pg/ml in 2 weeks compared with baseline ($16.2 \pm 3.4$ pg/ml). In the BJIKT group, mean plasma TxB₂ concentration changed $-13.6 \pm 3.6$ pg/ml in 2 weeks (Table 4). However, a statistically significant decrease in plasma TxB₂ was not detected in either the BJIKT or placebo groups. The inhibition of platelet aggregation at baseline and 1 and 2 weeks for the BJIKT and placebo groups combined with aspirin was accessed. In the placebo group, the platelet aggregation with 100 mg of aspirin was decreased to be $-0.2 \pm 5.1$% at 2 weeks compared with 74.8 $\pm 3.6$% at baseline. In the BJIKT group, the platelet aggregation was found to be $-1.1 \pm 2.8$% at 2 weeks compared with 73.6 $\pm 2.5$% at baseline. However, the combination of aspirin with either BJIKT or the placebo did not change the inhibition of collagen-induced platelet aggregation (Table 4).

**4. Discussion**

This is the first study to investigate the PK and PD profiles of the herb-drug interaction between BJIKT and aspirin among healthy subjects and patients with ischemic stroke. Overall, there were no apparent differences in the PK profiles of ASA and SA and PD profiles of TxB₂ and platelet aggregation between aspirin alone and coadministration with BJIKT among either healthy subjects or ischemic stroke patients, suggesting that BJIKT may not interact with aspirin.

The increased use of herbal medicines and supplements worldwide has substantially increased the number of potential drug interactions with modern drugs, and there has been the documented experimental and clinical evidence of interactions between herbal products and modern drugs [9]. Among these, herbs that may influence the effect of antiplatelet treatment are of particular interest, considering that treatment for coronary artery diseases and ischemic stroke is quite common, and aspirin is one of the drugs most frequently used to treat these diseases.

BJT may be prescribed for stroke caused by qi deficiency. It is also a typical prescription for deficiency of middle qi and overall symptoms of qi deficiency [16]. This prescription may tonify the spleen and raise and circulate pure qi, which is effective against fever, heart discomfort, sweating, fatigue, dizziness, numbness, and weakness [16]. BJIKT is composed of 10 natural herbs, among which Ginseng inhibited TxA₂ formation and thus platelet aggregation in *in vitro* studies [9, 17, 18] and impaired platelet aggregation in rats [19]. Astragalus could reduce platelet adhesion and aggregation, reduce plasma fibrinogen, and show antithrombus formation effect [10–12]. Glycyrrhiza can inhibit thrombin and platelet aggregation, therefore enhancing the risk of bleeding with antiplatelets and anticoagulants [4]. Hesperidin, which is major component of Citri Unshii Pericarpium, has been documented to inhibit TxB₂ formation and human platelet aggregation [14]. However, there are controversial reports that Ginseng inhibited CYP2D6, but the magnitude of the effect did not appear clinically relevant [20], and Citri Unshii demonstrated a relatively low frequency of drug interactions and had weak inhibitory effects on CYP2C9, which metabolizes NSAIDs [21, 22]. Furthermore, cocktail herbal medicine including Ginseng and Citrus, not single herb, indicated no significant effect on CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity in healthy volunteers [20]. Therefore, our results, along with previous reports, support the idea that BJIKT does not affect the antiplatelet effects of aspirin.

In the PK study, $C_{\text{max}}$, $T_{\text{max}}$, and $\text{AUC}$ of plasma ASA and SA were not changed by BJIKT among healthy subjects and ischemic stroke patients. And PD profiles showed no apparent differences in the TxB₂ and platelet aggregation between aspirin alone and coadministration with BJIKT among healthy subjects and even among ischemic stroke patients.

Most herb-drug interaction studies have used *in vitro* testing of herbal constituents in microsomal system or conducted in healthy subjects, but most relevant results have
been obtained when conducted in the patients who have used the herb and drug together. Thus, the advantage of this study is conducted with patients as well healthy subjects. However, BJIKT consist of 10 medicinal plants and contain multiple compounds, which may not accurately represent all the effects of each plant and/or compound. Moreover, the sample size of this study is relatively small and all participants are Korean, which may also have the limitation of applying study result to other races. Therefore, further study with large sample and various races should be required.

5. Conclusions

In conclusion, the PK and PD profiles of aspirin were not affected by combined treatment with BJIKT. No safety clinical concerns were raised among ischemic stroke patients. These results suggest that coadministration with BJIKT for the purpose of antiplatelet effects may not result in herb-drug interaction.

Disclosure

The authors are responsible for the writing and contents of the paper.

Conflicts of Interest

There are no conflicts of interest to declare.

Acknowledgments

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (H15C0133).

References

[1] G. N. Asher, A. H. Corbett, and R. L. Hawke, "Common herbal dietary supplement-drug interactions," American Family Physician, vol. 96, no. 2, pp. 101–107, 2017.
[2] M. de Lima Toccafondo Vieira and S.-M. Huang, "Botanical-drug interactions: a scientific perspective," Planta Medica, vol. 78, no. 13, pp. 1400–1415, 2012.
[3] A. Fugh-Berman, "Herb-drug interactions," The Lancet, vol. 355, no. 9198, pp. 134–138, 2000.
[4] A. Tachjian, V. Maria, and A. Jahangir, "Use of herbal products and potential interactions in patients with cardiovascular diseases," Journal of the American College of Cardiology, vol. 55, no. 6, pp. 515–525, 2010.
[5] X. Q. Wang, T. Takahashi, S. Zhu et al., "Effect of Hochu-ekki-to (TJ-41), a Japanese herbal medicine, on daily activity in a murine model of chronic fatigue syndrome," Evidence-Based Complementary and Alternative Medicine, vol. 1, no. 2, pp. 203–206, 2004.
[6] J.-N. K. In-Seon Choi and K. Young-Kyun, "Neurological effects of bojungikki-tang and bojungikki-tang-gamibang on focal cerebral ischemia of the MCAO rats," The Journal of Korean Oriental Medicine, vol. 30, no. 6, pp. 53–86, 2009.
[7] H. Kuratsune, "Effect of Kampo Medicine, "Hochu-ekki-to", on chronic fatigue syndrome," Clinic and Research, vol. 74, pp. 1837–1845, 1997.
[8] V. Scheid, D. Bensky, A. Ellis, and R. Barolet, Chinese herbal medicine: formulas strategies, Eastland Press, 2009.
[9] W. Abebe, "Herbal medication: potential for adverse interactions with analgesic drugs," Journal of Clinical Pharmacy and Therapeutics, vol. 27, no. 6, pp. 391–401, 2002.
[10] J. Gao, X. Xu, and S. Ni, "Research on antithrombotic effect of total saponins of astragalus," Chinese Traditional Patent Medicine, vol. 24, no. 2, pp. 116–118, 2002.
[11] Y. Xu, P. Gao, and Q. Liang, "Experimental study on effect of astragalus polysaccharide to the cerebral thrombosis," Chinese Journal of Hematology, vol. 9, no. 3, pp. 133–136, 1999.
[12] Q. Wang, J. Li, and Y. Liu, "Effect of astragalus injection on the formation of venous thrombosis in rats," Chinese Traditional Patent Medicine, vol. 25, no. 6, 498 pages, 2003.
[13] Y. Wu, J. Ouyang, and S. Tu, "Effects of Astragalus Polysaccharides on atherosclerosis endothelial cell injury," Journal of Hebei College of Traditional Chinese Medicine, vol. 4, no. 1, 21 pages, 2002.
[14] T.-H. Kim, H.-M. Kim, S. W. Park, and Y.-S. Jung, "Inhibitory effects of yuzu and its components on human platelet aggregation," Biomolecules & Therapeutics, vol. 23, no. 2, 149 pages.
[15] D. M. Becker, J. Segal, D. Vaidya et al., "Sex differences in platelet reactivity and response to low-dose aspirin therapy," The Journal of the American Medical Association, vol. 295, no. 12, pp. 1420–1427, 2006.
[16] J. Heo, Translated Dongeubigam, Translated Dongeubigam, Seoul, 1999.
[17] J. Gruenwald, T. Brendler, and C. Jaenicke, PDR for Herbal Medicines, Medical Economics Company, Inc, Montvale, NJ, USA, 1998.
[18] S.-C. Kuo, C.-M. Teng, J.-C. Lee, F.-N. Ko, S.-C. Chen, and T.-S. Wu, "Antiplatelet components in panax ginseng," Planta Medica, vol. 56, no. 2, pp. 164–167, 1990.
[19] H.-J. Park, J.-H. Lee, Y.-B. Song, and K.-H. Park, "Effects of dietary supplementation of lipophilic fraction from Panax ginseng on cGMP and cAMP in rat platelets and on blood coagulation," Biological & Pharmaceutical Bulletin, vol. 19, no. 11, pp. 1434–1439, 1996.
[20] B. J. Gurley, S. F. Gardner, M. A. Hubbard et al., "Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John’s wort, garlic oil, Panax ginseng and Ginkgo biloba," Drugs & Aging, vol. 22, no. 6, pp. 525–539, 2005.
[21] T. Fujita, A. Kawase, T. Niwa et al., "Comparative evaluation of 12 immature citrus fruit extracts for the inhibition of cytochrome P450 isozyme activities," Biological & Pharmacetical Bulletin, vol. 31, no. 5, pp. 925–930, 2008.
[22] J. Bigler, J. Whiton, J. W. Lamp, L. Fosdick, R. M. Bostick, and J. D. Potter, "CYP2C9 and UGT1A6 genotypes modulate the protective effect of aspirin on colon adenoma risk," Cancer Research, vol. 61, no. 9, pp. 3566–3569, 2001.