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ORIGINAL RESEARCH

Assessment of Pharmacokinetic Effects of Herbal Medicines on Escitalopram

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Purpose: Herbal medicines are occasionally used in combination with conventional antidepressants to mitigate various depression-associated symptoms. However, there is limited information on herb–antidepressant interactions. In this study, we investigated the pharmacokinetic (PK) effects of four herbal medicines (Gami-soyosan, Banhasasim-tang, Ojeok-san, and Bojungikgi-tang) on escitalopram, a commonly used antidepressant.

Patients and Methods: In this open-label, fixed-sequence, three-period, crossover study, 18 participants were enrolled and divided into two groups. Each group received a 10 mg oral dose of escitalopram in period 1. Participants took escitalopram once daily and their assigned herbal medicines thrice a day for 7 d in periods 2 (group 1: Gami-soyosan, group 2: Ojeok-san) and 3 (group 1: Banhasasim-tang; group 2: Bojungikgi-tang). The primary endpoints were $C_{max,ss}$ and $AUC_{tau,ss}$ of escitalopram. $C_{max,ss}$ and $AUC_{tau,ss}$ in period 1 were obtained using nonparametric superposition from single-dose data. The PK endpoints were classified according to the CYP2C19 phenotype.

Results: Of 18 participants, 16 completed the study. Systemic exposure to escitalopram resulted in a minor increase in the presence of each herbal medicine. The geometric mean ratios (GMRs, combination with herbal medicines/escitalopram monotherapy) and their 90% confidence intervals (CIs) for $C_{max,ss}$ and $AUC_{tau,ss}$ were as follows: Gamisoyosan– 1.1454 (0.9201, 1.4258) and 1.0749 (0.8084, 1.4291), Banhasasim-tang–1.0470 (0.7779, 1.4092) and 1.0465 (0.7035, 1.5568), Ojeok-san–1.1204 (0.8744, 1.4357) and 1.1267 (0.8466, 1.4996), and Bojungikgi-tang–1.1264 (0.8594, 1.4762) and 1.1400 (0.8515, 1.5261), respectively. Furthermore, no significant differences in the GMRs of $C_{max,ss}$ and $AUC_{tau,ss}$ were observed across different CYP2C19 phenotypes in any of the groups.

Conclusion: The co-administration of escitalopram with Gami-soyosan, Banhasasim-tang, Ojeok-san, or Bojungikgi-tang did not exert significant PK effects on escitalopram. These findings provide valuable insights into the safe use of herbal medicines along with escitalopram.

Keywords: CYP2C19 phenotype, herb–drug interaction, antidepressant, geometric mean ratio

Introduction

Depressive disorder is a psychiatric disease characterized by mood, cognition, and motor function symptoms, ultimately affecting an individual's working and social abilities.[1,2] The World Health Organization has emphasized the importance of diagnosing and treating depressive disorders owing to their emergence as a global public health concern.[3] It is estimated that depression will become the leading cause of global disease burden by 2030.[4] Failure to provide appropriate treatment for depressive symptoms can result in their persistence, leading to a decline in the patient's quality of life and difficulties in social functioning.

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly used drugs for treating depressive disorders. SSRIs include fluoxetine, escitalopram, paroxetine, citalopram, and others.[5] Serotonin is a monoamine neurotransmitter that reduces anxiety, depression, and aggression. Under normal circumstances, serotonin is released

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in the brain and is reabsorbed by presynaptic neurons at the synapse, effectively disappearing.[6] However, SSRIs block the reuptake process of serotonin by presynaptic neurons, allowing serotonin to remain in the brain for an extended period, accounting for their psychiatric effects.[5,6]

Among various SSRIs, escitalopram is frequently prescribed for depressive disorders. Escitalopram is an S-enantiomer of the racemate citalopram, another SSRI that was developed earlier. Escitalopram shows dose linearity within the range of 10–30 mg and has a half-life of approximately 27–32 h, achieving a steady-state within 7 d of daily dosing.[7] It is metabolized by the enzymes CYP2C19, CYP2D6, and CYP3A4, with a weak inhibitory effect on CYP2D6, making it prone to drug interactions when co-administered with other drugs.[8,9] It has been reported that CYP2C19 polymorphism significantly affects escitalopram metabolism.[10]

In 2018, the Traditional Korean Medicine Foundation reported that 73.8% of respondents in a survey on the use of traditional Korean medicine had experienced traditional Korean medical treatment.[11] Nearly 25% of herbal supplement users in the USA regularly consume prescribed medications.[12] In addition, patients can easily obtain herbal medicines without a doctor's prescription. Herbal medicines consist of various chemical substances from plants and other organisms, which increase the potential for interactions between synthetic pharmaceuticals and herbal medicines.[13,14] This interaction can diminish therapeutic effects or increase the risk of side effects.[14–16]

Patients with depressive disorders have a higher probability of taking herbal medicines than other patients.[17] In Korea, the herbal medicines commonly prescribed for depressive disorders include Gami-soyosan, Banhasasim-tang, Ojeok-san, and Bojungikgi-tang. Given the Korean medical system, there is a high probability of co-administration of SSRIs and herbal medicines. However, there are currently insufficient clinical data concerning the pharmacokinetic (PK) interactions of these herbal medicines when co-administered with escitalopram in humans. Consequently, there is a lack of substantiated evidence supporting the concurrent use of escitalopram with these herbal medicines.

Therefore, we aimed to investigate the PK effects of four herbal medicines (Gamisoyos-an, Banhasasim-tang, Ojeok-san, and Bojungikgi-tang) when co-administered with escitalopram and assessed whether these PK effects vary based on the CYP2C19 polymorphism.

Materials and Methods

Ethical Consideration

The study protocol was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2020-1400). It was registered with the Clinical Research Information Service (KCT0006117). This study was conducted in accordance with the Declaration of Helsinki and the Korean Good Clinical Practice guidelines. All participants provided written informed consent before enrollment in the study. The authors recognize that clinical trials should be registered prior to patient enrollment, and while the Clinical Research Information Service (CRIS) also recommends this, it does accept the registration of trials that have already been completed or are being conducted. This is the reason for the discrepancy in initial recruitment and registration date.

Participants

Data were prospectively collected from 18 healthy male participants. Eligible participants were healthy male adults aged 19–55 years with a body weight ≥55 kg and a body mass index between 18.5 and 27.0 kg/m^2. Patients with clinically significant diseases affecting the pulmonary, cardiovascular, hepatobiliary, neurological, endocrine, or immune systems were excluded. Additionally, the exclusion criteria included individuals with gastrointestinal diseases or surgeries affecting drug absorption and those with a clinically significant bleeding history.

Study Design

This was a two-sequence, multiple-dose, crossover, Phase 1 clinical trial. The dates of the trial period were from 15 Feb 2021 to 15 APR 2021. The investigational products included 10 mg of escitalopram or a combination of escitalopram and each herb. All four herbal medicines were standardized products based on the criteria in pharmacopoeia published by the Ministry of Food and Drug Safety. They were purchased from Hanpoong Pharmaceutical Co.,

Ltd., which have Good Manufacturing Practice guidelines. Each sequence group consisted of three treatments in different orders. On day 1 of period 1, all participants received a single oral dose of 10 mg escitalopram tablets (E). Blood samples for PK evaluation were collected at specified time points: pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 24, 48, 72, and 96 h. On day 2 of period 1, blood samples were collected to assess the CYP2C19 phenotype. During periods 2 and 3, participants received a 10 mg escitalopram tablet orally once daily, in combination with one packet of either herbal medicine thrice per day for 7 d: for Group 1, Gami-soyosan (E+A1; period 2)–Banhasasim-tang (E+A2; period 3), and for Group 2, Ojeok-san (E+A3; period 2)–Bojungikgi-tang (E+A4; period 3). During periods 2 and 3, blood samples for PK were collected at pre-dose, 1, 2, 3, 4, 5, 8, 10, and 24 h on day 1; pre-dose on days 5 and 6; and at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 24, 48, 72, and 96 h on day 7. The washout periods were 7 d (between periods 1 and 2) and 14 d (between periods 2 and 3).

Plasma Assay for PK and CYP2C19 Phenotype

For the measurement of escitalopram plasma concentration, approximately 6 mL of blood was collected in tubes containing EDTA-K2 and centrifuged at 3000 rpm and 4°C for 10 min. Following centrifugation, the supernatant was preserved at −70°C or lower. Escitalopram concentrations were analyzed using liquid chromatography-mass spectrometry (Acquity UPLC, Waters; API 3200, AB Sciex).[18] The calibration range was 1.0–100.0 ng/mL, with a correlation coefficient of ≥0.9995. The lower limits of quantification (LLOQ) for these assays were 1.0 ng/mL. Accuracy within the range of 85–115% (LLOQ: 80–120%) was observed for both intra- and inter-day assays, and all precisions exhibited a coefficient of variation of <15% (LLOQ: <20%).

For the analysis of CYP2C19 phenotypes, approximately 2 mL of blood was collected in tubes containing EDTA-K2 and subsequently analyzed. Participants were categorized as extensive metabolizers (EM), intermediate metabolizers (IM), or poor metabolizers (PM) based on their CYP2C19 genotype, following the guidelines of the Clinical Pharmacogenetics Implementation Consortium guideline.[19] Specifically, we analyzed the *2 and *3 alleles to assess CYP2C19 activity deficiency and the *17 allele to assess increased CYP2C19 activity.

PK Analysis

All PK parameters were obtained using a noncompartmental analysis with WinNonlin® 8.0 or updated version.[20] For each treatment group, descriptive statistics, including the number of participants, arithmetic means, and standard deviations, were calculated.

The primary endpoints were the maximum escitalopram concentration at steady-state ($C_{max,ss}$) and the area under the plasma concentration–time curve within a dosing interval at steady-state ($AUC_{tau,ss}$). The secondary endpoints were $AUC_{inf,ss}$, $AUC_{last,ss}$, and time to maximum concentration at steady state ($T_{max,ss}$) for escitalopram. C_{max} and T_{max} were the actual values, and the AUC was calculated using the trapezoidal rule. The half-life ($t_{1/2}$), apparent volume of distribution (Vd/F), and apparent clearance (CL/F) were calculated using the data and the AUC. In period 1, when only escitalopram was administered, the PK parameters at steady-state were obtained using the nonparametric superposition method.[21] This approach was used because all participants received a single dose of escitalopram during this period. $C_{max,ss}$ and $AUC_{tau,ss}$ values were transformed into natural logarithms. The point estimate and 90% confidence interval (CI) of the mean difference in log-transformed $C_{max,ss}$ and $AUC_{tau,ss}$ between escitalopram monotherapy and the co-administration of escitalopram with each herbal medicine were estimated. Furthermore, in addition to the total participants in each group, the PK effects of each herbal medicine on escitalopram stratified by the CYP2C19 phenotype were evaluated.

Safety

Safety evaluations were conducted by confirming adverse events (AEs), including vital signs, laboratory tests, electrocardiograms, and physical examinations and by reporting subjective symptoms. All AEs that occurred during the trial were recorded using the terms defined in the MedDRA ver. 24.0.

Results

Baseline Characteristics

The baseline demographics of the participants in each group are shown in Table S1. Of the 27 individuals who participated in the screening, 18 were included in the clinical trial and randomized into two groups with nine participants in each group. Among them, 16 participants completed the entire clinical trial, while two participants in group 1 withdrew during period 3.

Regarding CYP2C19 phenotypes, group 1 had four EM, four IM, and one PM. Group 2 included five EM and four IM participants, with no PM participants identified. Therefore, the PK parameters stratified by the CYP2C19 phenotype were analyzed, comparing EM + IM participants to PM participants.

PK Effect of Each Herbal Medicine on Escitalopram

The time-concentration profile of escitalopram at steady state showed slightly higher concentrations in the co-administration therapy group than those in the E-alone group (Figure 1).

The escitalopram PK parameters after treatment at steady state and after the first dose are summarized in Tables 1 and S2, respectively. The $T_{max,ss}$ values were approximately 2–3 h for all the treatments. Within each group, both $C_{max,ss}$ and $AUC_{tau,ss}$ values of escitalopram in the co-administration therapy group showed a minor increase and were slightly higher than those observed with E alone.

The point estimates of the GMRs (co-administration/E only) and their corresponding 90% confidence intervals for $C_{max,ss}$ and $AUC_{tau,ss}$ of escitalopram are summarized in Table 2. When escitalopram was co-administered with each

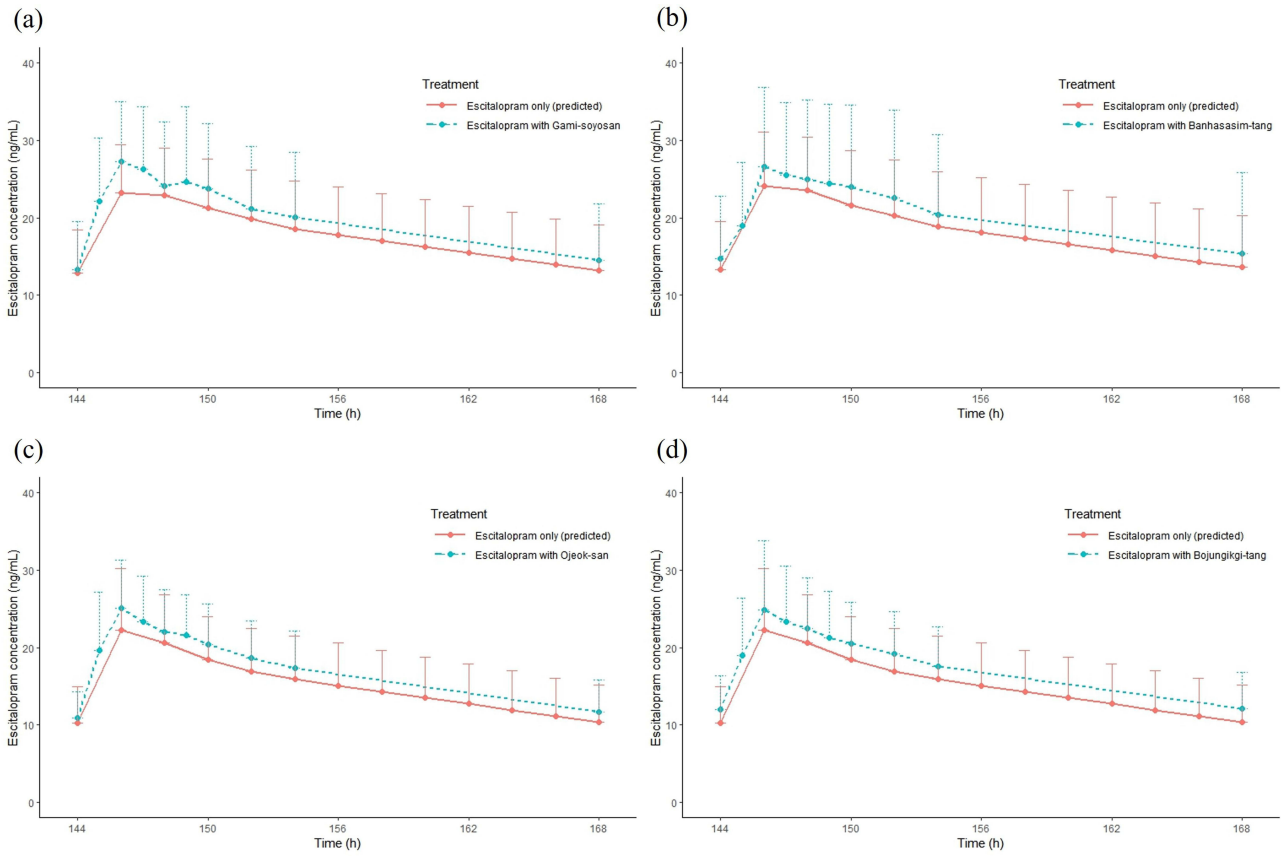

Figure 1 Time–concentration profile of escitalopram at steady state when escitalopram was only administered and co-administered with (**a**) Gami-soyosan (n=9), (**b**) Banhasasim-tang (n=7), (**c**) Ojeok-san (n=9), and (**d**) Bojungikgi-tang (n=9). Each point and line represents mean, and the bar represents standard deviation.

Table 1 Summary of Plasma Escitalopram PK Parameters by Treatment at Steady State

Parameters	Group 1			Group 2		
	E* (n=9)	E+A1 (n=9)	E+A2 (n=7)	E* (n=9)	E+A3 (n=9)	E+A4 (n=9)
$T_{max,ss}$ (h)	2.0 (2.0–4.0)	2.0 (1.0–5.0)	3.0 (2.0–8.0)	2.0 (2.0–4.0)	2.0 (1.0–2.0)	2.0 (2.0–5.9)
$C_{max,ss}$ (ng/mL)	24.1±5.8	28.1±8.9	27.0±10.4	23.0±7.3	25.3±6.3	25.8±8.1
$AUC_{tau,ss}$ (h·ng/mL)	427.7±145.5	468.0±190.7	477.7±246.1	365.7±131.9	401.7±115.3	408.5±127.5
$AUC_{last,ss}$ (h·ng/mL)	–	1033.4±613.9	1086.1±840.8	–	790.8±307.9	814.2±355.0
$AUC_{inf,ss}$ (h·ng/mL)	–	1270.6±992.9	1340.1±1263.3	–	888.6±368.6	910.9±429.3
Vd_{ss}/F (L)	–	1028.9±163.3	981.4±158.0	–	1000.1±192.4	962.4±188.4
CL_{ss}/F (L/h)	–	24.1±8.2	5.2±10.6	–	26.9±8.3	26.7±8.4

Notes: E* PK parameters at steady state were estimated using the nonparametric superposition method. All data are expressed as mean±standard deviation except $T_{max,ss}$, median (min–max).

Abbreviations: E, 10 mg tablet of escitalopram orally once in fasting; E+A1, 10 mg tablet of escitalopram orally once daily with Gami-soyosan, one packet thrice day for 7 d; E+A2, 10 mg tablet of escitalopram orally once daily with Banhasasim-tang, one packet thrice a day for 7 d; E+A3, 10 mg tablet of escitalopram orally once daily with Ojeok-san, one packet thrice a day for 7 d; E+A4, 10 mg tablet of escitalopram orally once daily with Bojungikgi-tang, one packet thrice a day for 7 d. $T_{max,ss}$, time at steady state when maximum plasma concentration is reached; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{tau,ss}$, area under the plasma drug concentration–time curve over a dosing interval at steady state; $AUC_{last,ss}$, area under the plasma drug concentration–time curve until the last time after the last dose at steady state; $AUC_{inf,ss}$, area under the plasma drug concentration–time curve after the last dose at steady state extrapolated to infinity; $AUC_{inf,ss}$; Vd_{ss}/F, the apparent volume of distribution at steady state; CL_{ss}/F, the apparent clearance at steady state.

Table 2 Geometric Mean Ratio and Its 90% Confidence Interval Between Only Escitalopram Administration and Co-Administration of Escitalopram with Each Herbal Medicine

Group	Treatment	Parameters	GeoLSM		GMR (90% CI)
			E	E+A1	E+A1/E
1	E vs E+A1 (n=9)	$C_{max,ss}$ (ng/mL)	23.5	27.0	1.1454 (0.9201, 1.4258)
		$AUC_{tau,ss}$ (h·ng/mL)	408.2	438.8	1.0749 (0.8084, 1.4291)
			E	**E+A2**	**E+A2/E**
	E vs E+A2 (n=7*)	$C_{max,ss}$ (ng/mL)	24.3	25.5	1.0470 (0.7779, 1.4092)
		$AUC_{tau,ss}$ (h·ng/mL)	413.9	433.1	1.0465 (0.7035, 1.5568)
2			**E**	**E+A3**	**E+A3/E**
	E vs E+A3 (n=9)	$C_{max,ss}$ (ng/mL)	21.9	24.6	1.1204 (0.8744, 1.4357)
		$AUC_{tau,ss}$ (h·ng/mL)	343.1	386.6	1.1267 (0.8466, 1.4996)
			E	**E+A4**	**E+A4/E**
	E vs E+A4 (n=9)	$C_{max,ss}$ (ng/mL)	21.9	24.7	1.1264 (0.8594, 1.4762)
		$AUC_{tau,ss}$ (h·ng/mL)	343.1	391.2	1.1400 (0.8515, 1.5261)

Notes: *Two participants in group 1 were excluded after period 2 completion.

Abbreviations: E, 10 mg tablet of escitalopram orally once in fasting; E+A1, 10 mg tablet of escitalopram orally once daily with Gami-soyosan, one packet thrice a day for 7 d; E+A2, 10 mg tablet of escitalopram orally once daily with Banhasasim-tang, one packet thrice a day for 7 d; E+A3, 10 mg tablet of escitalopram orally once daily with Ojeok-san, one packet thrice a day for 7 d; E +A4, 10 mg tablet of escitalopram orally once daily with Bojungikgi-tang, one packet thrice a day for 7 d; GeoLSM, geometric least squares mean; GMR, geometric least squares mean ratio; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{tau,ss}$, area under the plasma drug concentration–time curve over a dosing interval at steady state.

herbal medicine, $C_{max,ss}$ and $AUC_{tau,ss}$ of escitalopram were approximately 1.05–1.15-fold higher than those of E alone, but there were no significant differences.

Moreover, we compared the PK parameters between co-administration and E monotherapy stratified by CYP2C19 phenotype (Table 3). Regardless of the herbal medicines co-administered, there was a slight tendency toward higher escitalopram exposure in individuals with the IM phenotype than in those with the EM phenotype. However, overall, the

Table 3 Geometric Mean Ratio and Its 90% Confidence Interval Between Only Escitalopram Administration and Co-Administration of Escitalopram with Herbal Medicine Stratified by CYP2C19 Phenotype

Group	Treatment	CYP2C19 Phenotype	Parameters	GeoLSM		GMR (90% CI)
				E	E+A1	E+A1/E
1	E vs E+A1 (n=8)	EM	$C_{max,ss}$ (ng/mL)	21.46	22.69	1.0574 (0.7600–1.4712)
			$AUC_{tau,ss}$ (h·ng/mL)	346.88	355.48	1.0248 (0.6766–1.5522)
		IM	$C_{max,ss}$ (ng/mL)	23.27	27.95	1.2013 (0.9634–1.4980)
			$AUC_{tau,ss}$ (h·ng/mL)	413.40	453.75	1.0976 (0.8441–1.4273)
	E vs E+A2 (n=6*)			E	E+A2	E+A2/E
		EM	$C_{max,ss}$ (ng/mL)	21.46	21.38	0.9966 (0.6958–1.4276)
			$AUC_{tau,ss}$ (h·ng/mL)	346.88	334.68	0.9648 (0.6256–1.4880)
		IM	$C_{max,ss}$ (ng/mL)	25.86	26.92	1.0413 (0.6321–1.7153)
			$AUC_{tau,ss}$ (h·ng/mL)	439.45	483.71	1.1007 (0.6499–1.8641)
2	E vs E+A3 (n=9)			E	E+A3	E+A3/E
		EM	$C_{max,ss}$ (ng/mL)	23.00	24.09	1.0476 (0.7043–1.5583)
			$AUC_{tau,ss}$ (h·ng/mL)	353.64	374.10	1.0579 (0.6698–1.6708)
		IM	$C_{max,ss}$ (ng/mL)	20.63	25.14	1.2185 (0.8163–1.8190)
			$AUC_{tau,ss}$ (h·ng/mL)	330.42	402.84	1.2192 (0.7626–1.9490)
	E vs E+A4 (n=9)			E	E+A4	E+A4/E
		EM	$C_{max,ss}$ (ng/mL)	23.00	24.65	1.0719 (0.6959–1.6513)
			$AUC_{tau,ss}$ (h·ng/mL)	353.64	393.18	1.1118 (0.6971–1.7731)
		IM	$C_{max,ss}$ (ng/mL)	20.63	24.73	1.1983 (0.7699–1.8651)
			$AUC_{tau,ss}$ (h·ng/mL)	330.42	388.63	1.1762 (0.7260–1.9055)

Notes: *Two participants in Group 1 were excluded after the completion of period 2. One participant in Group 1 was a PM.

Abbreviations: E, 10 mg tablet of escitalopram orally once in fasting; E+A1, 10 mg tablet of escitalopram orally once daily with Gami-soyosan, one packet thrice a day for 7 d; E+A2, 10 mg tablet of escitalopram orally once daily with Banhasasim-tang, one packet thrice a day for 7 d; E+A3, 10 mg tablet of escitalopram orally once daily with Ojeok-san, one packet thrice a day for 7 d; E+A4, 10 mg tablet of escitalopram orally once daily with Bojungikgi-tang, one packet thrice a day for 7 d; GeoLSM, geometric least squares mean; GMR, geometric least squares mean ratio; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{tau,ss}$, area under the plasma drug concentration–time curve over a dosing interval at steady state.

exposure levels in the co-administration therapy group were similar to those observed with E alone. There was only one participant with PM in Group 1. For PM, and $AUC_{tau,ss}$ of escitalopram in combination with herbal medicine were about 1.2–1.3 times higher than those in E alone: $C_{max,ss}$–35.72, 46.54, and 46.06 ng/mL in E, E+A1, and E+A2, respectively; $AUC_{tau,ss}$–744.07, 890.13, and 974.25 h·ng/mL, respectively.

Safety

Among the 18 participants, 21 AEs were reported in nine participants. Specifically, there were five AE cases in the E group, one in the E+A1 group, two in the E+A2, eight in the E+A3, and five in the E+A4 group. Of the 21 AEs, 18 were associated with the study drugs. Of these, 16 AEs were classified as mild, while 5 AEs were considered moderate. No serious AEs were observed. Moderate AEs included one case of acute hepatitis in the E+A1 group and two cases each of drug eruption and dermatitis in the E+A3 and E+A4 groups. Most of the AEs resolved without complications or sequelae. One participant withdrew from the study because of acute hepatitis and diarrhea (AE); however, it was also reported to have resolved. There were no clinically significant abnormalities in vital signs, laboratory tests, electrocardiograms, or physical examinations, except for AEs. The details of the AEs are described in Table S3.

Discussion

Worldwide, including Korea, many patients co-administer synthetic pharmaceuticals and herbal medicines.[22,23] However, there is the potential for herb–drug interactions (HDIs) between synthetic pharmaceuticals and herbal medicines. Furthermore, considering that many herbal medicines have not undergone preclinical and clinical studies for HDIs and can be purchased without prescription by doctors, the presence of HDIs in humans has not been identified.

In depressive disorders, many patients take antidepressant drugs, such as SSRIs, along with herbal medicines more often than other patients.[17] The four herbal medicines selected (Gami-soyosan, Banhasasim-tang, Ojeok-san, and Bojungikgi-tang) have many beneficial effects in improving depressive symptoms. Gami-soyosan is produced from soyo-san by adding Gardeniae Fructus and Moutan Radicis Cortex. It has been used to improve the symptoms of sleep disturbance, headache, and dizziness and to reduce stress.[24] However, details of these substances and their mechanisms of action are rarely known.[25] Banhasasim-tang has been widely used to treat dyspepsia and gastroesophageal reflux.[26,27] Ojeok-san improves heartburn associated with gastroesophageal reflux.[28] A previous study has shown that it has the potential as an analgesic to ameliorate visceral sensitivity and reduce abdominal pain.[29] Bojungikgi-tang is a traditional oriental herbal formula comprising eight medicinal herbs. It has been used to treat gastric disorders, such as gastric atony, smooth muscle asthenia, and stomach muscle asthenia.

However, these herbal medicines are associated with CYP450 enzymes. According to several in vitro evaluations, Gami-soyosan has a weak inhibitory effect on CYP1A2,[30] whereas Banhasasim-tang has no significant effect on CYP450 enzymes.[31] Ojeko-san has an inhibitory effect on CYP1A2 and CYP2D6 but has a relatively weak inhibition of CYP2C9, CYP2C19, CYP2E1, and CYP3A4.[32] Bojungikgi-tang inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[33] Accordingly, HDIs are possible when a patient is concurrently administered herbal medicines along with other drugs.

Escitalopram, an SSRI commonly prescribed for depressive disorders, is a substrate of several CYP450 enzymes and a weak inhibitor of CYP2D6.[8,9] Escitalopram has a high possibility of HDIs and numerous PK interactions, leading to significant side effects and complications, have been described with herbal and plant preparations. For instance, interactions with milk thistle, ginkgo, ginseng, and Rhodiola rosea have been reported. Combinations of escitalopram with each preparation resulted in cough, ejaculation disorders, bleeding, priapism, myalgia, or ventricular arrhythmia.[34] In another study, interactions with Withania somnifera and Tribulus terrestris have been reported. This study demonstrated that the combination of escitalopram and Withania somnifera caused myalgia, epigastric pain, nausea, vomiting, restless legs syndrome, and severe cough, while the combination of escitalopram and Tribulus terrestris led to galactorrhea. Possible interaction mechanisms include the inhibition of P-glycoprotein, CYP3A4 and CYP2D6.[35] There are also reports of interactions of escitalopram and marijuana derivatives. Co-administration of escitalopram with tetrahydrocannabinol or cannabidiol significantly increased the $t_{1/2}$, AUC_{24} and C_{max} of escitalopram by inhibiting cytochrome activity.[36] Therefore, in this study, we examined whether these four herbal medicines had significant PK effects on escitalopram. We selected this drug for depressive disorders because patients with depressive symptoms would like to take herbal medicines more than other patients.[17]

This clinical trial used an open-label, fixed-sequence, three-period, crossover design. Although escitalopram was administered by single dosing in period 1 because escitalopram follows linear PK at 10 mg, nonparametric superposition is suitable for estimating PK parameters at steady state in drugs with linear PK.[7,21] The 7-d multiple-dosing period for the co-administration of escitalopram and herbal medicines was adequate to establish a steady state of escitalopram, considering that the $T_{1/2}$ of escitalopram ranges from approximately 19 to 33 h. In addition, a duration of 7 d was appropriate based on the consideration of the time required to induce or inhibit CYP enzymes. The time required to achieve maximum CYP enzyme induction typically spans 7–14 d.[37] This was supported by a previous study that assessed the PK effects of Ojeok-san on celecoxib administered for 8 d, validating the appropriateness of our dosing duration.[38]

In this study, it was identified that $C_{max,ss}$ and $AUC_{tau,ss}$ of escitalopram in combination with herbal medicine were 1.05–1.15-fold higher than those of E alone. This may be due to the inhibitory effects of herbal medicines on CYP450 enzymes. However, these differences were not statistically significant. There were no serious AEs and/or clinically significant abnormalities in the vital signs, laboratory tests, electrocardiograms, or physical examinations. Therefore,

there were no significant PK effects of the herbal medicines on escitalopram, and no safety concerns regarding the concurrent use of these herbal medicines with escitalopram.

In addition, to test whether CYP2C19 polymorphisms affect the magnitude of PK effects, we determined the PK parameters stratified by each CYP2C19 phenotype. For all herbal medicines, the GMRs in the IM were higher than those in the EM. In particular, for Gami-soyosan (only $C_{max,ss}$), Ojeok-san, and Bojungikgi-tang, the GMR values were close to 1.25. However, as same as all participants, because when GMRs and their 90% CIs were in the range of 0.8–1.25, there were no significant PK effects of each herbal medicine on escitalopram in both EM and IM. Therefore, the differences in the PK effects between EM and IM were not significant. For PM, $C_{max,ss}$ and $AUC_{tau,ss}$ of escitalopram in combination with herbal medicine were approximately 1.2–1.3 times higher than those of E alone. The magnitudes of the increases were similar to those of other phenotypes, and the PK effects of each herbal medicine on escitalopram were not significant in PM.

This study had several limitations. First, there were only 18 participants with nine in each group. Considering that this study was not confirmatory but exploratory, it was appropriate to study a small group. Second, for escitalopram administration only, PK parameters at steady state were obtained using data after single dosing by the nonparametric superposition method.[21] Although the nonparametric superposition method simulates concentrations at a steady state based on data after a single dose, they differ from actual values obtained from sampling after multiple doses. However, this may not have had a significant effect on the results, because escitalopram follows a linear PK at 10 mg. Third, we did not explore the PK effects of escitalopram on the four herbal medicines; therefore, we could not evaluate the complete PK HDIs because of the one-way evaluation. This was due to the difficulty in the PK analysis of herbal medicines because many herbal medicines lack reliable assays to measure concentration, although there are many herbal medicines with validated analytical methods.[39] If appropriate assays for these herbal medicines are developed, studies can be conducted to assess the effects of escitalopram on herbal medicines. Finally, there was an insufficient number of participants with each CYP phenotype (especially only one participant with PM and no participant with an ultra-metabolizer). Nevertheless, our study is meaningful because it is an exploratory analysis to identify the PK effects of herbal medicines on escitalopram. Due to the limitations mentioned above, subsequent studies with more participants are needed to confirm and reinforce our findings.

In this study, we only assessed the effects of four herbal medicines on escitalopram. However, other herbal medicines are often co-administered with SSRIs. Furthermore, SSRIs other than escitalopram are commonly prescribed for treating depressive symptoms. Therefore, further studies are needed to assess whether PK HDIs exist between other SSRIs and herbal medicines.

Conclusion

This study demonstrated that the co-administration of escitalopram with Gami-soyosan, Banhasasim-tang, Ojeok-san, and Bojungikgi-tang did not exert significant effects on escitalopram. These findings provide valuable insights into the safe use of herbal medicines along with escitalopram. However, due to some limitations, further studies are required to validate our results.

Data Sharing Statement

- Whether the authors intend to share individual deidentified participant data: Yes.
- What specific data they intend to share: All of the individual participant data collected during the trial, after deidentification.
- What other study-related documents will be made available: Synopsis of study protocol and clinical study report.
- How the data will be accessible: If requesting, available from the corresponding author.
- When and for how long they will be made available: Immediately following publication. No end dates.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Current affiliation for Dr Yun Seob Jung is at the Department of Convergence Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea. The authors report no conflicts of interest in this work.

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