A Comprehensive In Vivo and In Vitro Assessment of the Drug Interaction Potential of Red Ginseng

Sook Jin Seong, MD[1,*]; Woo Youl Kang, MD[1,2,*]; Jae-Kyung Heo, MS[3,4,5]; Jungjae Jo, MS[3,4,5]; Won Gu Choi, MS[6]; Kwang-Hyeon Liu, PhD[3,4,5]; Sangkyu Lee, PhD[3,4,5]; Min-Koo Choi, PhD[7]; Yong-Hae Han, PhD[8]; Hye Suk Lee, PhD[6]; Boram Ohk, MS[1,2]; Hae Won Lee, MD[1]; Im-Sook Song, PhD[3,5]; and Young-Ran Yoon, MD, PhD[1,2]

[1]Clinical Trial Center, Kyungpook National University Hospital, Daegu, Republic of Korea; [2]Department of Biomedical Science, BK21 Plus KNU Bio-Medical Convergence Program for Creative Talent, Graduate School, Kyungpook National University, Daegu, Republic of Korea; [3]Research Institute of Pharmaceutical Sciences, Daegu, Republic of Korea; [4]BK21 Plus KNU Multi-Omics Based Creative Drug Research Team, Daegu, Republic of Korea; [5]College of Pharmacy, Dankook University, Cheon-an, Republic of Korea; [6]College of Pharmacy, The Catholic University of Korea, Bucheon, Republic of Korea; [7]College of Pharmacy, Dankook University, Republic of Korea; and [8]Life Science Institute, Daewoong Pharmaceutical, Yongin, Gyeonggi-do, Republic of Korea

ABSTRACT

Purpose: Red ginseng is one of the world's most popular herbal medicines; it exhibits a wide range of pharmacologic activities and is often co-ingested with other herbal and conventional medicines. This open-label, randomized, 3-period study investigated the in vivo herb−drug interaction potential for red ginseng extract with cytochrome P-450 (CYP) enzymes and organic anion-transporting polypeptide (OATP) 1B1.

Methods: Fifteen healthy male volunteers (22-28 years; 57.1-80.8 kg) were administered a single dose of cocktail probe substrates (caffeine 100 mg, losartan 50 mg, omeprazole 20 mg, dextromethorphan 30 mg, midazolam 2 mg, and pitavastatin 2 mg) and single or multiple doses of red ginseng extract for 15 days.

Findings: The pharmacokinetic profiles of the probe substrates and metabolites after single- or multiple-dose administration of red ginseng extracts were comparable to the corresponding profiles of the control group. The geometric mean ratio of AUC_{0-t} and 90% CIs for the probe substrate drugs between the control and multiple doses of red ginseng for 15 days were within 0.8 to 1.25 (CYP2C9, CYP3A4, and OATP1B1 probe substrates) or slightly higher (CYP1A2, CYP2C19, and CYP2D6 probe substrates). Additional assessments of the in vitro drug interaction potential of red ginseng extracts and the ginsenoside Rb1 on drug-metabolizing enzymes and transporters using human liver microsomes, cryopreserved human hepatocytes, and transporter-overexpressed cells were negative.

Implications: Red ginseng poses minimal risks for clinically relevant CYP- or OATP-mediated drug interactions and is well tolerated. Clinical Research Information Service registry no.: (*Clin Ther*. 2018;■:1−16) © 2018 Elsevier Inc. All rights reserved.

Key words: cytochrome P450, drug interaction, OATP1B1, pharmacokinetics, red ginseng.

INTRODUCTION

Ginseng (*Panax ginseng* C.A. Meyer [Araliaceae]) has been one of the most popular herbal medicines

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worldwide for >2000 years; it is especially popular in East Asian countries, including the Republic of Korea, China, and Japan.[1,2] Among the 3 types of cultivated ginseng (fresh ginseng, white ginseng, and red ginseng), red ginseng is produced from fresh ginseng grown for 6 years through the processes of steaming and drying, which lead to biochemical transformations in the constituent peptides, ginsenosides, polysaccharides, fatty acids, and polyacetylenic alcohols.[3] Ginsenosides, also known as steroid-like saponins, are considered the major active pharmacologic constituents of ginseng.[1,4] Ginseng and its associated ginsenosides reportedly have antineoplastic, antihypertensive, antidiabetic, anti-inflammatory, antioxidative, antiallergic, neuroprotective, hepatoprotective, and immunologic effects.[4–7] After consumption of red ginseng products, the ginsenosides Rb1, Rb2, Rc, Rd, Rg1, Rg3, Rh1, and Re were found in the human gut and plasma.[8,9] Among these ginsenosides, Rb1 is the most abundant and stable, with a long elimination $t_{1/2}$ of 58.47 hours.

Although a variety of in vitro and in vivo pharmacokinetic (PK) interaction studies between fresh ginseng and cytochrome P-450 (CYP) enzymes have been reported,[10–13] to date, limited in vitro or in vivo studies have been performed to determine the effect of red ginseng on CYP enzymes.[14] Furthermore, according to a literature search, the present study is the first to evaluate the effect of red ginseng on the activity of the organic anion-transporting polypeptide (OATP) 1B1 transporter in vivo and in vitro.

The objective of the present study therefore was to investigate the in vivo effect of red ginseng on the activities of major human CYP enzymes and the drug transporter OATP1B1 by using respective probe drugs (ie, caffeine for CYP1A2, losartan for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6, midazolam for CYP3A, pitavastatin for OATP1B1). The study also evaluated the in vitro drug interaction potential of red ginseng and the major ginsenoside Rb1 by monitoring the inhibitory effects and induction potentials of red ginseng and Rb1 on drug-metabolizing enzymes and transporters in human liver microsomes, transporter-overexpressed cells, and cryopreserved human hepatocytes.

SUBJECTS AND METHODS

Study Subjects and Design

The study protocol was approved by the institutional review board of Kyungpook National University Hospital (KNUH; Daegu, Republic of Korea). The study was conducted at the KNUH Clinical Trial Center, in accordance with the ethical standards of the Declaration of Helsinki and the applicable Good Clinical Practice guideline. Written informed consent was obtained from all subjects before their participation in this study.

Healthy Korean male volunteers aged ≥19 years, who weighed ≥50 kg, and whose weight was within ±20% of their ideal body weight, were eligible to participate in this study. No subject had clinically significant abnormalities as confirmed by clinical history, a detailed physical examination, routine clinical laboratory tests (hematology, biochemistry, and urinalysis), serology tests (hepatitis B surface antigens, anti–hepatitis C virus antibody, anti-HIV antibody, and the Venereal Disease Research Laboratory test), and 12-lead ECG, conducted within 4 weeks before study drug administration.

This open-label, randomized, 3-period, single-sequence study was conducted in healthy male adult volunteers (Figure 1). In period 1 (day 1), each subject received a single oral dose of the probe drug cocktail, which contained caffeine (100 mg),* losartan (50 mg),† omeprazole (20 mg),‡ dextromethorphan (30 mg),§ midazolam (2 mg),‖ and pitavastatin (2 mg)¶ as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and OATP1B1 substrates, respectively.[15] After a 7-day washout period, in period 2 (day 8), subjects received 3 pouches of concentrated red ginseng extract (Hongsamjung All day, Lot No. 731902; dried ginseng >60%) (Punggi Ginseng Cooperative Association, Youngjoo, Kyungpook, Republic of Korea) and a single dose of the probe drug cocktail orally. On days 9 to 21 of period 2, all subjects received 3 pouches of red ginseng extract once daily. In period 3 (day 22), each subject received a single dose of the probe drug cocktail and 3 pouches of red ginseng extract orally.

*Trademark: JET-ALERT® (Bell Pharmaceuticals Inc., Belle Plaine, Minnesota).

†Trademark: Cozaar® (MSD Korea Ltd, Seoul, Republic of Korea).

‡Trademark: Losec® (Yuhan Corporation, Seoul, Republic of Korea).

§Trademark: Tussin Cough® (CVS Pharmacy Inc, Woonsocket, Rhode Island).

‖Trademark: midazolam Inj®. (Bukwang Pharm Co, Ltd, Seoul, Republic of Korea).

¶Trademark: Livalo® (JW Pharmaceutical, Seoul, Republic of Korea).