A randomized, double-blind, placebo-controlled pilot study to assess the effects of protopanaxadiol saponin–enriched ginseng extract and pectinase-processed ginseng extract on the prevention of acute respiratory illness in healthy people

Jeong-Hwan Hwang1,2,3, q, Soo-Hyun Park4, q, Eun-Kyung Choi4, Su-Jin Jung4, Mi Kyung Pyo6, Soo-Wan Chae4,5, *

1 Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, Jeonbuk, Republic of Korea
2 Research Institute of Clinical Medicine of Jeonbuk National University, Jeonju, Jeonbuk, Republic of Korea
3 Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Jeonbuk, Republic of Korea
4 Clinical Trial Center for Functional Foods, Jeonbuk National University Hospital, Jeonju, Jeonbuk, Republic of Korea
5 Department of Pharmacology, Jeonbuk National University Medical School, Jeonju, Jeonbuk, Republic of Korea
6 International Ginseng and Herb Research Institute, Geumsan, Republic of Korea

ABSTRACT

Background: GS-3K8 and GINST, both of which are modified ginseng extracts, have never been examined in terms of their effectiveness for the prevention of acute respiratory illness (ARI) in humans. We conducted a pilot study to assess the feasibility of performing a large-scale, randomized, controlled trial.

Methods: This study was a randomized, double-blind, placebo-controlled, pilot study at a single center from October 2014 to March 2015. The 45 healthy applicants were randomly divided into the GS-3K8 (n = 15), GINST (n = 15), and placebo groups (n = 15). The study drug was administered as a capsule (500 mg/cap and 3000 mg/day). GS-3K8 contained 6.31 mg/g of Rg1, 15.05 mg/g of Re, 30.84 mg/g of Rb1, 15.02 mg/g of Rc, 12.44 mg/g of Rb2, 6.97 mg/g of Rd, 1.59 mg/g of Rg3, 3.25 mg/g of Rk1, and 4.84 mg/g of Rg5. GINST contained 7.54 mg/g of Rg1, 1.87 mg/g of Re, 5.42 mg/g of Rb1, 0.29 mg/g of Rb2, 0.70 mg/g of Rd, and 6.3 mg/g of compound K. The feasibility criteria were the rates of recruitment, drug compliance, and successful follow-up. The primary clinical outcome measure was the incidence of ARI. The secondary clinical outcome measures were the duration of symptoms.

Results: The rate of recruitment was 11.3 participants per week. The overall rate of completed follow-up was 97.8%. The mean compliance rate was 91.64 ± 9.80%, 95.28 ± 5.75%, and 89.70 ± 8.99% in the GS-3K8, GINST, and placebo groups, respectively. The incidence of ARI was 64.3% (9/14; 95% confidence interval [CI], 31.4–91.1%), 26.7% (4/15; 95% CI, 4.3–49.0%), and 80.0% (12/15; 95% CI, 54.8–93.0%) in the GS-3K8, GINST, and placebo groups, respectively. The average days of symptoms were 3.89 ± 4.65, 9.25 ± 7.63, and 12.25 ± 12.69 in the GS-3K8, GINST, and placebo groups, respectively.

Conclusion: The results support the feasibility of a full-scale trial. GS-3K8 and GINST appear to have a positive tendency toward preventing the development of ARI and reducing the symptom duration. A randomized controlled trial is needed to confirm these findings.

* Corresponding author. Department of Pharmacology, Jeonbuk National University Medical School, 567 Baekje-daero, Deokjin-gu, Jeonju-si, Jeolla-buk-do, 54896, Republic of Korea.
q Jeong-Hwan Hwang and Soo-Hyun Park contributed equally to this work.

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1. Introduction

Acute respiratory illness (ARI) is mainly caused by respiratory viruses, and its progression is self-limiting [1]. However, it leads to reduced functioning and work productivity [2]. ARI is also associated with a marked economic burden to the health-care system and society because of medical costs and lost work time [3]. According to the Korean Health Insurance Review and Assessment Service, the cost of medical care for ARI was approximately 920 million dollars per year from 2007 to 2011 and approximately 1.4 billion dollars per year from 2012 to 2016 [4].

Infections caused by respiratory viruses, particularly influenza and respiratory syncytial virus, remain a significant cause of death in community-dwelling older adults [5]. Influenza vaccination may have limited efficacy in this population because of an age-associated decrease in both humoral and cell-mediated immune function [6]. In addition, the use of amantadine and rimantadine is limited by their side effects and the development of resistance [7]. Although neuraminidase inhibitors do not have these limitations, the cost of these drugs has been the greatest barrier to their use in institutional settings [7].

Ginseng products, including Korean ginseng and American ginseng, are available over the counter and are often used for the prevention and treatment of ARI [8,9]. Recently, we showed the preventive effects of Korean ginseng on the development of ARI [8]. However, there is insufficient evidence to conclude that standard ginseng extracts decrease the incidence of ARI [1]. Therefore, modified ginseng extracts that have changes in the composition or absorbability of ginsenosides, which are mainly attributed to the pharmacological effects of ginseng, are needed [10].

Ginsenoside Rb1, one of the protopanaxadiol (PPD)-type ginsenosides, suppresses viral infection and the proliferation of various viruses in vitro [11–13]. PPD-type ginsenosides Rb1, Rb2, and Rc are transformed into compound K by the intestinal microflora [14]. GINST is a modified ginseng extract that hydrolyzes these ginsenosides into pectinase and enhances the absorption of component K [15]. GS-3K8 is another modified ginseng extract with enhanced PPD-type ginsenoside content [16]. There has been no large-scale, randomized, controlled study on the preventive effects of GS-3K8 and GINST against ARI. Therefore, we conducted a pilot study on GS-3K8 and GINST to determine the feasibility of a larger study.

2. Materials and methods

2.1. Study design

This pilot study was conducted as a randomized, double-blind, placebo-controlled trial to assess the feasibility of a large, randomized, controlled trial to compare GS-3K8 and GINST with placebo. The trial was conducted at the Clinical Trial Center for Functional Foods at Jeonbuk National University Hospital, which is a 1,200-bed, university-affiliated teaching hospital and the largest referral center in Jeollabuk-do, a province of Korea. Volunteers were informed about the study, including the study protocol, after which the study physician obtained informed consent from each participant. The screening examination was conducted within 4 weeks of the study initiation. The participants who passed the screening process were randomly allocated into one of the three groups (GS-3K8, GINST, or placebo) with an allocation ratio of 1:1:1. Random numbers were generated using the block randomization method in the Microsoft Office Excel 2007 program (Microsoft Corporation, Redmond, WA, USA) for sequence generation. The randomization sequence and allocation were concealed from all study participants, research staff, investigators, and pharmacists until the completion of the study.

At the first visit, the enrolled participants were instructed to ingest two capsules three times per day (after every meal) for 12 weeks. All participants were educated regarding ARI and instructed to contact the investigators and study physician at the onset of a cold. The participants were instructed not to consume any ginseng products other than those provided for the study or other functional foods or dietary supplements. During the study period, the participants who developed ARI received symptomatic treatment under the direction of the study physician. They were instructed not to take any other cold medication unless advised by the study physician. Every 6 weeks, the participants were asked to report any adverse events or adverse drug reactions, changes in lifestyle or eating patterns, and symptoms of ARI and assess their drug compliance. Laboratory tests were performed at the first visit and 12-week visit. During the 12-week intervention period and 6-week follow-up period, ARI-related symptoms were assessed weekly via telephone. If any symptoms were reported to the study physician, telephone interviews were then conducted daily until the symptoms ended.

2.2. Study population

The participants were recruited through media advertisements, and those volunteers were screened via a telephone interview for the inclusion and exclusion criteria. The participants were eligible to participate in this study if they were in good general health and aged between 39 and 65 years. The participants were excluded based on the following criteria: (1) vaccinated against influenza in the previous 6 months, (2) upper respiratory tract infection at the time of screening, (3) underlying medical conditions such as human immunodeficiency virus infection, malignancy, and cardiovascular, pulmonary, hepatic, renal, neurological, psychiatric, autoimmune, or hematologic diseases, (4) alcohol abuse or drug addiction, (5) gastrointestinal diseases, such as Crohn’s disease, that may interrupt the absorption of the test drug or gastrointestinal surgery, except herniotomy and appendectomy, (6) taking immunomodulators such as immunosuppressants or immunostimulants, (7) hypersensitive to ginseng or currently taking ginseng, (8) participation in another clinical study within 2 months of the screening test, (9) abnormal hepatic or renal test, (10) psychological conditions making it difficult to participate in a study, and (11) pregnant or lactating.

2.3. Study drugs

GS-3K8, the PPD saponin–enriched ginseng extract used in this study, was obtained from the International Ginseng & Herb Research Institute (Geumsan, Republic of Korea) and prepared as described previously with slight modifications [16]. The preparation method of GS-3K8 was as follows: Ginseng material was prepared from mixtures of ginseng main root and rootlet (root:rootlet = 4:6). Ginseng mixture (1 kg) was extracted with 10 L of water at 80°C for 6 hours. Each extraction was repeated three times. The obtained water extract was concentrated up to 80% of extraction volume by ultrafiltration system with a 3-kDa hollow fiber cartridge. Inner fraction of the ginseng extract obtained by ultrafiltration system was further dried in a freeze dryer for the preparation of PPD saponin–enriched ginseng extract and then named as GS-3K8. GS-3K8 contained 6.31 mg/g of Rg1, 15.05 mg/g of Rg5, 30.84 mg/g of Rb1, 15.02 mg/g of Rb2, 12.44 mg/g of Rb2, 6.97 mg/g of Rb1, 15.95 mg/g of Rg3, 3.25 mg/g of Rg5, and 4.84 mg/g of G5. GINST, a pectinase-processed Panax ginseng extract, was obtained from ILHWA Co. Ltd., (Guri, Republic of Korea) and prepared...
as described previously with slight modifications [15]. The preparation method of GINST was as follows: Dried ginseng (1 kg) was extracted in 5 L of 50% ethanol in water and concentrated with a vacuum concentrator. The dry ginseng extract was incubated with an enzyme solution containing 2.4% pectinase (Sigma-Aldrich, St Louis, MO, USA) at 55 °C for 24 hours. GINST contained 7.54 mg/g of Rg1, 1.87 mg/g of Re, 5.42 mg/g of Rb1, 0.29 mg/g of Rc, 0.36 mg/g of Rb2, 0.70 mg/g of Rd, and 6.3 mg/g of compound K [17]. The placebo capsule was composed primarily of maltodextrin, soybean oil, palm oil, lecithin, rice bran wax, cacao color, and annatto extract and was matched to the other capsules with regard to energy content, flavor, appearance, and dosage. The study drug capsules were packaged indistinguishably and labeled with the participant’s number. The compositions of the study drugs are shown in Table 1. The participants were instructed to bring all remaining supplements at each visit, and good compliance was defined as 75% or greater. The study drug was supplied to the participants two times, at the first visit and 6-week visit.

2.4. Outcome measures

All outcome measures were defined a priori. The primary outcome measures for this pilot study were the recruitment rate, follow-up rate, and drug compliance rate. The three feasibility objectives would be considered successful if we achieved a recruitment rate of ≥11 participants per week, completed follow-ups for at least 95% of all recruited participants, and a mean compliance rate of 90% or greater. Completed follow-up was defined as the percentage of randomized participants who completed all assessments during the 18-week study period. Compliance was defined as follows: percent compliance = 100 × (number of capsules dispensed – number of capsules returned)/number of capsules prescribed. The secondary outcome measures were the clinical outcome measures that would be used in a large-scale clinical study. The primary clinical outcome was the incidence of ARI, and the secondary clinical outcome was the duration of ARI-related symptoms.

2.5. Safety assessment and tolerability

Safety was assessed through the number of adverse events and adverse drug reactions that were measured using the results of

| Component, mg (%) | GS-3K8 | GINST | Placebo |
|-------------------|--------|-------|---------|
| Protopanaxadiol saponin-enriched ginseng extract | 162 (32.53) | - | - |
| Pectinase-processed ginseng extract | - | 160 (31.94) | - |
| Maltodextrin | - | - | 160 (32.00) |
| Soybean oil | 238 (47.79) | 243 (48.50) | 241 (48.10) |
| Palm oil | 40 (8.03) | 40 (7.98) | 30 (6.00) |
| Rice bran wax | 50 (10.04) | 50 (9.98) | 48 (9.60) |
| ER 290 | 8 (1.61) | 8 (1.60) | - |
| Lecithin | - | - | 11 (2.30) |
| Annatto extract | - | - | 3 (0.60) |
| Cacao color | - | - | 7 (1.40) |
| Total | 498 (100) | 501 (100) | 500 (100) |

Fig. 1. Flow chart showing the number of participants assessed for eligibility, randomization, follow-up, and analysis.
laboratory tests and vital signs. Tolerability was evaluated through the side effects of GS-3K8, GINST, and placebo capsules. Specifically, the participants were asked about gastrointestinal symptoms, such as nausea, vomiting, loss of appetite, gastrointestinal distress, and intolerance to certain tastes, at each visit.

### 2.6. Ethical approval

The protocol for this study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB number: 2014-02-011) and registered at www.clinicaltrials.gov (NCT03028077).

### 2.7. Sample size and data analysis

Because preliminary data were lacking regarding the ability of GK-3K8 or GINST to prevent ARI in healthy people, a pilot trial was performed to generate preliminary data for the design of a large-scale clinical trial. Continuous variables were expressed as the mean value and standard deviation, and categorical variables were expressed as the percentage. The cumulative risk of ARI was estimated using the Kaplan–Meier method. Hazard ratios and 95% confidence intervals (CIs) comparing the incidence rate between GS-3K8 and placebo or between GINST and placebo were estimated using Cox proportional hazards regression models. Calculations of sample size were based on the ability to detect a 20% difference in the event rates of ARI between the GS-3K8 and placebo groups with 80% power using a two-sided p value of 0.017 by Bonferroni correction. SPSS software (version 19.0; IBM, Chicago, Illinois, USA) was used for all statistical analyses.

### 3. Results

Fig. 1 describes the management of the participants in this pilot study. The participants were recruited at the Clinical Trial Center for Functional Foods at Jeonbuk National University Hospital, Jeollabuk-do, Republic of Korea, in October 2014. The rate of recruitment in this feasibility study was 11.3 participants per week. Initially, 49 participants were enrolled in the study; however, four participants did not meet the inclusion criteria and were excluded. The remaining 45 participants were randomly allocated to the GS-3K8 (n = 15), GINST (n = 15), and placebo (n = 15) groups. The participants in each group took the study drug during the 12-week intervention period and were assessed for ARI occurrence during the next 6 weeks (follow-up period). During the study period, one participant in the GS-3K8 group withdrew consent, and the remaining 44 of the 45 randomized participants were followed up for the entire study period, yielding a follow-up rate of 97.8%.

The demographic characteristics of the participants are presented in Table 2, and Table 3 presents the clinical events, that is, primary and secondary clinical outcomes, observed in this study. The incidence of ARI was 64.3% (9/14; 95% CI, 31.4–91.1%) in the GS-3K8 group, 26.7% (4/15; 95% CI, 4.3–49.0%) in the GINST group, and 80.0% (12/15; 95% CI, 54.8–93.0%) in the placebo group. The average number of days of symptoms were 3.89 ± 4.65, 9.25 ± 7.63, and 12.25 ± 12.69 in the GS-3K8, GINST, and placebo groups, respectively. The Kaplan–Meier plots in Fig. 2 show the cumulative incidence of ARI in the GS-3K8, GINST, and placebo groups. The hazard ratio of ARI was 0.59 (95% CI, 0.28–1.22) in the GS-3K8 group and 0.25 (95% CI, 0.01–0.64) in the GINST group. Statistical comparisons between the groups for clinical outcomes were not conducted because this pilot study was not powered for such comparisons and any statistical conclusions from such comparisons would be misleading.

### 4. Discussion

The mean compliance rate was 91.64 ± 9.80% in the GS-3K8 group, 95.28 ± 5.75% in the GINST group, and 89.70 ± 8.99% in the placebo group (Table 4). The percentage of participants achieving 75% or greater compliance was 92.9% in the GS-3K8 group and 100% in the GINST and placebo group. There were no adverse drug reactions reported in the GS-3K8, GINST, or placebo groups. Five adverse events were observed: one case of herpes zoster in the GS-3K8 group, one case each of herpes zoster and radial styloid tenosynovitis in the GINST group, and one case each of vaginitis and rhinitis in the placebo group. Gastrointestinal intolerance and taste intolerance were not observed in the GS-3K8, GINST, or placebo groups. During the study period, vital signs were measured and laboratory tests were performed for the safety assessment, and the results are shown in Tables 5 and 6.

### Table 2

Demographic characteristics of the study participants.

| Variables        | GS-3K8 group (n = 15) | GINST group (n = 15) | Placebo group (n = 15) |
|------------------|----------------------|----------------------|------------------------|
| Sex, n (%)       | Male 1 (6.7)         | 2                     | 0                      |
|                   | Female 14 (93.3)     | 13                    | 15 (100)               |
| Age, mean, y     | 54.47 ± 3.40         | 55.00 ± 2.95          | 53.00 ± 3.66           |
| Height, mean, cm | 159.07 ± 6.86        | 159.27 ± 8.88         | 158.13 ± 5.08          |
| Body weight, mean, kg | 60.89 ± 6.93      | 64.26 ± 10.32         | 58.82 ± 2.78           |
| BMI, mean, kg/m² | 24.09 ± 2.30         | 25.24 ± 2.73          | 23.58 ± 2.78           |
| Alcohol drinking, n (%) | 5 (33.3)        | 7 (46.7)               | 7 (46.7)               |
| Yes              | 10 (66.7)            | 8 (53.3)               | 8 (53.3)               |
| No               | 15 (100)             | 15 (100)              | 14 (93.3)              |

BMI, body mass index.

### Table 3

Number of clinical events observed in each group.

| Variables              | GS-3K8 group (n = 14) | GINST group (n = 15) | Placebo group (n = 15) |
|------------------------|-----------------------|----------------------|------------------------|
| Primary clinical outcome, n (%; 95% CI) | ARI 9 (64.3; 31.4–91.1) | 4 (26.7; 4.3–49.0) | 12 (80.0; 54.8–93.0) |
| Secondary clinical outcomes, n, mean days ± SD | Sore throat 0 1, 2 | 5, 3.80 ± 2.49 | 3, 5.00 ± 3.00 | 6, 8.50 ± 3.25 |
|                        | Coryza 7, 2.57 ± 1.13 | 3, 5.00 ± 3.00 | 4, 6.00 ± 2.76 | 3, 7.67 ± 2.73 |
|                        | Nasal congestion 0 0 | 0 0 0 | 6, 4.00 ± 2.76 | 3, 7.67 ± 2.73 |
|                        | Sneezing 6, 2.33 ± 1.03 | 0 0 | 0 0 0 | 5, 10.00 ± 9.25 |
|                        | Hoarseness 2, 1.10 ± 0.00 | 1 1 1 | 2, 2.00 ± 0.00 | 1 1 1 |
|                        | Myalgia 1, 1 | 0 0 0 | 0 0 0 | 0 0 0 |
|                        | Otalgia 0 0 | 0 0 0 | 0 0 0 | 0 0 0 |
|                        | Fever 0 0 | 1, 1 | 1, 1 1 | 4, 6.00 ± 6.06 |
|                        | Headache 1, 1 | 0 0 | 0 0 0 | 0 0 0 |
|                        | Cough 3, 7.00 ± 6.93 | 0 0 0 | 7, 10.43 ± 12.63 | 4, 6.00 ± 6.06 |
| Total                  | 9, 3.89 ± 4.65 | 4, 9.25 ± 1.22 | 12, 12.25 ± 12.69 | 4, 6.00 ± 6.06 |

ARI, acute respiratory illness; CI, confidence interval; SD, standard deviation.
consumption of ≥75% of the study drug). The reasons for this high compliance are that the study participants were interested in health supplements such as Korean Red Ginseng. Korean Red Ginseng is readily available in everyday life, and the participants did not experience drug intolerance or adverse drug reactions in this study. A similar previous study in our center has a compliance rate of more than 90% [8]. However, the definition of good compliance in this study is somewhat arbitrary because the use of categories such as “good” and “poor” compliance is not supported, as noted by the appropriateness of the cutoff for specific medications in [18].

We achieved our target follow-up rate and successfully followed up 97.8% (44/45) of the randomized participants. The recruitment rate in this study was modest, with 11.3 participants per week. However, most studies on the effects of ginseng on the prevention of ARI did not report the recruitment rates. A previous large-scale randomized controlled trial performed in our center recruited 12.5 participants per week, and another large-scale RCT on Panax quinquefolius recruited 36.6 participants per week [8,19]. The results from this pilot study suggest that a sample of 345 participants (115 in each group) would be required to progress to a full-scale RCT in the future, which allows for a 5% loss of participants during the follow-up period. If a full-scale RCT was conducted in a single center, recruitment would take 7–8 months. However, if the number of centers was doubled, we estimate that full recruitment would be achieved in approximately 4 months.

The protective effects of Panax ginseng against infection caused by viruses, such as respiratory syncytial virus, rhinovirus, and influenza virus causing upper respiratory tract infections, have been shown previously in several experimental data [20]. Some RCTs have documented the clinically favorable effects of standard ginseng extract, including Panax quinquefolius or Panax ginseng, on ARI [8,21]. Recently, a study on Panax ginseng at our institution showed a reduction in the incidence and symptom duration of ARI [8]. However, in other research, Panax quinquefolius did not show a protective effect against ARI [5]. In addition, previous studies of Panax quinquefolius or Panax ginseng on ARI in humans have shown insufficient evidence on their effectiveness in preventing ARI [22]. GINST is a modified ginseng extract with an increased content of compound K formed by fermentation of PPD-type ginsenosides Rb1, Rb2, and Rc by pectinase [14]. By increasing the content of compound K by fermentation, GINST showed excellent pharmacokinetic parameters in a human study rather than the usual nonfermented ginseng extract [15]. GINST showed higher antiviral activity against a variety of influenza viruses than nonfermented ginseng extract [23]. GS-3K8 also showed an antiviral activity against influenza virus A (H1N1) as a modified ginseng extract with a high proportion of Rb1/Rg1 by increasing the content of PPD-type ginsenosides via ultrafiltration [24].

Therefore, we conducted a pilot-scale human participant study using GS-3K8 and GINST, which are made from standard ginseng

| Variables                  | GS-3K8 group (n = 14) | GINST group (n = 15) | Placebo group (n = 15) |
|----------------------------|-----------------------|----------------------|------------------------|
| Compliance                 |                       |                      |                        |
| Capsules prescribed, mean ± SD | 498.14 ± 6.49         | 499.20 ± 8.13        | 502.80 ± 8.44          |
| Capsule intake, mean ± SD  | 456.21 ± 46.36        | 475.73 ± 31.04       | 451.20 ± 47.59         |
| Compliance rate, %, mean ± SD | 91.64 ± 9.80         | 95.28 ± 5.75         | 89.70 ± 8.99           |
| Achieved ≥75% compliance, n (%) | 13 (92.9)           | 15 (100)             | 15 (100)               |
| Tolerability               |                       |                      |                        |
| Gastrointestinal intolerance, n | 0                    | 0                    | 0                      |
| Taste intolerance, n       | 0                     | 0                    | 0                      |

SD, standard deviation.

Fig. 2. Kaplan–Meier estimates of the cumulative risk of acute respiratory illness in the GS-3K8 and GINST groups compared with the placebo group.
extracts by changing the composition or absorbability of ginsenosides and their enzymatic or heat-processed metabolites such as compound K. This study did not test a formal hypothesis, but this feasibility study found a sufficient number of participants to achieve statistical power is warranted to demonstrate the protective effects of GS-3K8 and GINST against ARI.

**Conflicts of interest**

The authors declare no conflicts of interest.

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