ORIGINAL ARTICLE

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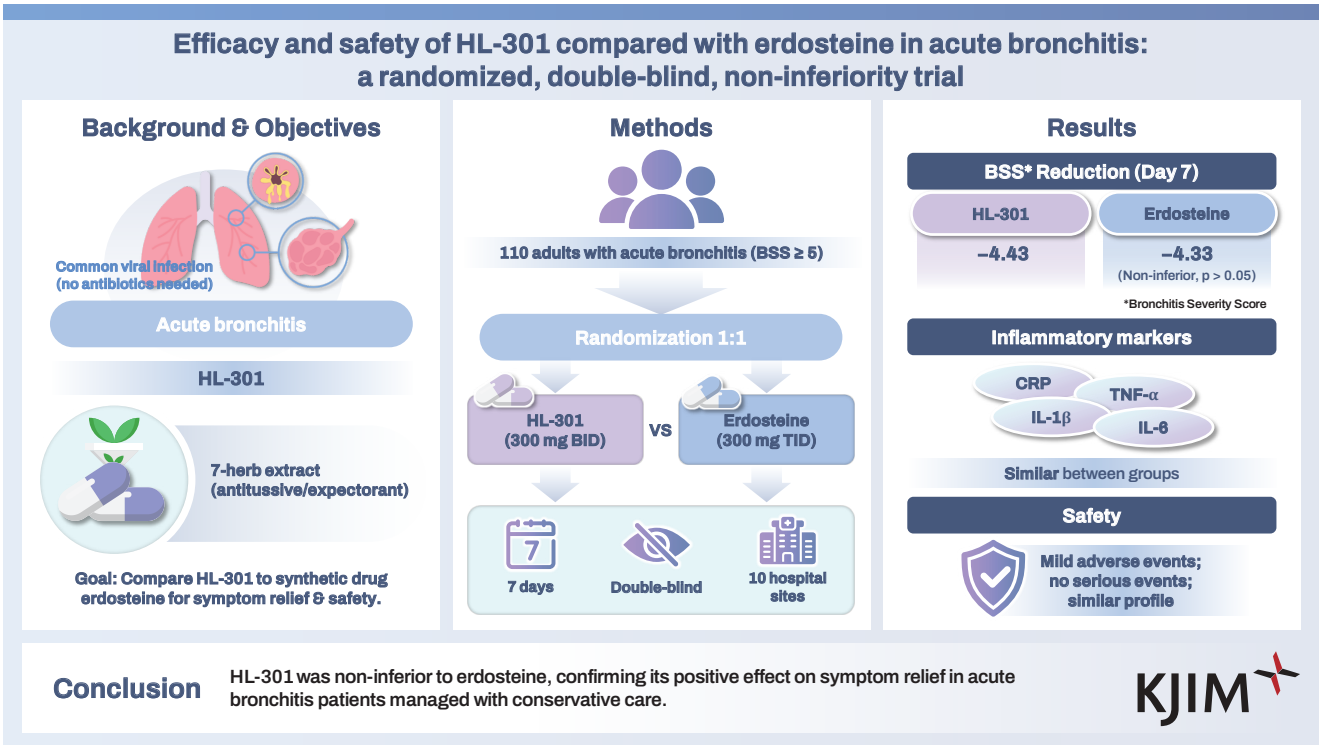
Efficacy and safety of HL-301 compared with erdosteine in acute bronchitis: a randomized, double-blind, non-inferiority trial

Ji-Yong Moon[1,*], Joon Young Choi[2,*], Youlim Kim[1], Hye Jung Park[3], Yong Bum Park[4], Seong Yong Lim[5], Kyung Hoon Min[6], Deog Kyeom Kim[7], Chin Kook Rhee[8], Seung Won Ra[9], Chang Youl Lee[10], Yong Il Hwang[11], and Kwang Ha Yoo[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [3]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; [4]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul; [5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [6]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Seoul; [7]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, College of Medicine, Seoul National University, Seoul; [8]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [9]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan; [10]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon; [11]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, College of Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea

*These authors contributed equally to this manuscript.



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Background/Aims: This study evaluated the non-inferiority of HL-301 to erdosteine in terms of symptom relief and the anti-inflammatory effects in acute bronchitis patients not treated with antibiotics.
Methods: In a double-blind, non-inferiority trial, patients were randomized 1:1 to receive either HL-301 (300 mg twice daily) or erdosteine (300 mg three times daily) for seven days. The primary endpoint was change in total Bronchitis Severity Score (BSS) from baseline to day 7. The non-inferiority margin was set at -0.99 for the difference in BSS change. The secondary endpoints were changes in specific symptoms, overall improvement, patient satisfaction, and inflammatory markers.
Results: Mean BSS reduction at day 7 was -4.43 in the HL-301 group (n = 53) and -4.33 in the erdosteine group (n = 52). The difference in mean BSS change between the groups was 0.11, with the lower limit of the 97.5% one-sided confidence interval at -0.42, confirming non-inferiority. The improvement in specific symptoms, overall improvement, and patient satisfaction were high in both groups; however, there were no significant differences between the groups. Additionally, the changes in C-reactive protein, tumor necrosis factor-alpha, interleukin (IL)-1β, and IL-6 were similar between the groups, with no significant differences observed. The incidence of adverse events was higher in the HL-301 group compared to the erdosteine group, including gastrointestinal disorder, periodontitis, and increased blood cholesterol, although this difference was not statistically significant.
Conclusions: HL-301 was non-inferior to erdosteine, confirming its positive effect on symptom relief in acute bronchitis patients managed with conservative care.

Keywords: Bronchitis; Expectorants; Clinical trial; Safety

INTRODUCTION

Bronchitis, characterized by inflammation of the bronchial mucosa, impairs normal bronchial function and presents with cough and sputum production [1]. Acute bronchitis, primarily caused by viral or bacterial infections, shows symptoms such as cough, body aches, and fever [2]. Patients with a cough lasting up to three weeks are diagnosed with acute bronchitis after ruling out conditions such as pneumonia [3]. According to the American College of Chest Physicians, acute bronchitis is one of the top 10 most common diseases, with an annual incidence rate of 5%, leading to about five outpatient visits per 100 people [4]. In South Korea, more than 15 million patients are treated annually for acute bronchitis, making it the most common outpatient disease and contributing significantly to increasing medical expenses [1].

Treatment of acute bronchitis focuses on symptom relief [4]. Because 90% of cases are viral, antibiotics are generally unnecessary. However, antibiotics are used in 70% of cases, leading to issues such as gastrointestinal disturbances, allergic reactions, increased treatment duration due to resistant bacteria, and higher recurrence risks, without reducing disease duration [1,5]. Thus, alternative therapies that improve patient discomfort without side effects are needed, and herbal medicine could be a suitable option.

HL-301 is an antitussive and expectorant medication composed of a soft extract from seven herbal ingredients: *Rehmannia glutinosa*, Moutan Cortex, *Schisandra chinensis*, *Asparagus cochinchinensis*, Armeniacae semen, *Scutellaria baicalensis*, and *Stemona japonica* [6-8]. Clinical trials have demonstrated that HL-301 is superior to placebo in improving the symptoms of patients with acute bronchitis or chronic bronchitis exacerbations [6]. Subsequent phase 2b trials confirmed the efficacy and safety of the 600 mg/d dose [7]. Additionally, phase 3 trial results indicated that HL-301 is non-inferior to the commercially marketed *Pelargonium* in terms of safety and efficacy for improving acute bronchitis symptoms [8].

Comparative studies on the symptom improvement and anti-inflammatory effects of synthetic drugs and herbal medicine for acute bronchitis are scarce. This study compares the efficacy of HL-301, an herbal medicine, with that of erdosteine, a widely used synthetic drug for mucolytic and expectorant treatment in acute and chronic respiratory diseases [9,10]. The study aim was to demonstrate the non-inferiority and safety of HL-301 compared with erdosteine in relieving the symptoms of patients with acute bronchitis and to evaluate improvements in specific symptoms, including sputum production and anti-inflammatory effects.

METHODS

Study design

This study was a multicenter, active-controlled, parallel-group, randomized, double-blind, non-inferiority trial conducted in patients with acute bronchitis. Patients were recruited from 10 hospitals in South Korea. Eligible participants were randomly assigned in a 1:1 ratio to receive either HL-301 (investigational drug, 300 mg twice daily) or erdosteine (control drug, 300 mg three times daily) for seven days. The investigational products, HL-301 and placebo, were supplied by Hanlim Pharm. Co. Ltd., Seoul, Republic of Korea. Block randomization was employed to ensure balanced allocation between the treatment and control groups, enhancing the internal validity of the trial. The randomization process was conducted using an Interactive Web Response System, which automated the allocation and maintained allocation concealment by preventing any potential investigator bias. The software used for randomization and data management was SAS® (Ver. 9.4, SAS Institute Inc.). Randomized participants were given the investigational drug and a placebo of the control drug or the control drug and a placebo of the investigational drug in a double-blind manner. Evaluator blindness was maintained by using identical placebos for both the investigational and control drugs, ensuring that neither evaluators nor participants could distinguish between treatment groups and thus preventing assessment bias. They took all medication three times daily: both the assigned medication and placebo in the morning and evening and the control drug or its placebo at noon.

During the study period, if participants experienced symptoms such as fever above 39°C, unbearable headache, or body aches, they were instructed to take a rescue medication (acetaminophen 650 mg), with a maximum dosage of two tablets per dose, up to three times a day (every eight hours) as needed.

Study participants

The inclusion criteria for this study required patients to have a Bronchitis Severity Score (BSS) of 5 or higher at both the screening visit and the first day of administration of the study drugs. Patients aged 19 to 80 years who developed symptoms of acute bronchitis within 48 hours prior to the screening visit were included.

The exclusion criteria were respiratory and systemic infections requiring systemic antibiotic treatment, peptic ulcer disease at screening, coagulation disorders or bleeding, severe pulmonary disease, creatinine clearance < 25 mL/min, or level of aspartate aminotransferase or alanine aminotransferase (ALT) that exceeded three times the upper limit of normal at screening. Additionally, patients who received systemic corticosteroids or immunosuppressants within four weeks prior to the first dose and those who used antiviral drugs, systemic/inhaled corticosteroids, mucolytics, expectorants, antitussives, herbal medicines with antitussive/expectorant effects, or antihistamines within 48 hours prior to the first dose were excluded. Patients with liver cirrhosis, cystathionine synthase deficiency, alcohol addiction, or heavy smoking habits and those who were pregnant or breastfeeding were also excluded.

Efficacy and safety evaluation

The primary efficacy endpoint was change in total BSS from baseline to day 7 of HL-301 or erdosteine treatment. The BSS comprises five acute bronchitis symptoms: cough, sputum production, dyspnea, chest pain during coughing, and wheezing/rhonchi. The investigator assessed the severity of each symptom on a scale from 0 to 4, according to the evaluation guidelines. The total BSS ranges from 0 to 20, with higher scores indicating more severe symptoms.

The secondary efficacy endpoints were change in individual BSS symptom scores from baseline to day 7, the investigator's overall assessment of improvement in clinical response at day 7, patient satisfaction with the treatment response, number rescue medications, and changes in inflammatory markers (C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-α], interleukin-1β [IL-1β], interleukin-6 [IL-6]) from baseline to day 7.

The safety evaluation involved monitoring all adverse events that occurred after drug administration and assessing changes in laboratory test results, vital signs, and physical examination findings from baseline to day 7.

Statistical analysis

The primary objective of this study was to demonstrate the non-inferiority of HL-301 to erdosteine in terms of changes in BSS after seven days of treatment. The sample size was calculated based on the results from the HL-301 phase 3 trial and the Synatura phase 2 trial and assuming a pooled standard deviation of 1.72 [11]. The non-inferiority margin was set at 0.99. With a one-sided significance level of 2.5%, 80% power, and a 5% dropout rate, the required sample

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size was 52 patients per group, totaling 104 patients.

Efficacy data obtained from the participants were primarily analyzed using the per protocol set (PPS) and additionally analyzed using the full analysis set (FAS), which included those who completed the primary efficacy evaluation in the safety set. Safety and demographic data were analyzed in the safety set, which included all participants who received at least one dose of the investigational or control drug.

For continuous data, the number of participants and mean, standard deviation, median, minimum, and maximum values are presented. The normality of the data distribution was tested, and comparisons between two groups used Student's t-test or Wilcoxon rank sum test. Pre- and post-treatment comparisons were performed using the paired t-test or Wilcoxon signed rank test. Additionally, an analysis of covariance (ANCOVA) was conducted with baseline values as covariates to compare the two groups.

For categorical data, the number of participants, percentages, and frequencies are presented, and comparisons between groups were conducted using the Chi-square test or Fisher's exact test. The primary efficacy evaluation involved calculating the lower limit of the 95% two-sided confidence interval (CI) (97.5% one-sided CI) for the difference in BSS change from baseline to day 7 between the HL-301 and erdosteine groups. If the lower limit was greater than -0.99, HL-301 was considered non-inferior to erdosteine.

All analyses were performed using available data without imputing missing values. A p value less than 0.05 was considered statistically significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute).

Ethics statement

The protocol for this study was reviewed and approved by the Institutional Review Board of Konkuk University Medical Center (approval No. 2021-12-026). Informed consent was submitted by all subjects at enrollment. The study procedures followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. This study was registered at ClinicalTrials.gov (NCT06038084).

RESULTS

Study subjects

Overall, 112 participants were screened for this study (Fig. 1). Two participants were excluded due to ALT level exceeding three times the upper limit of normal, resulting in 110 par-

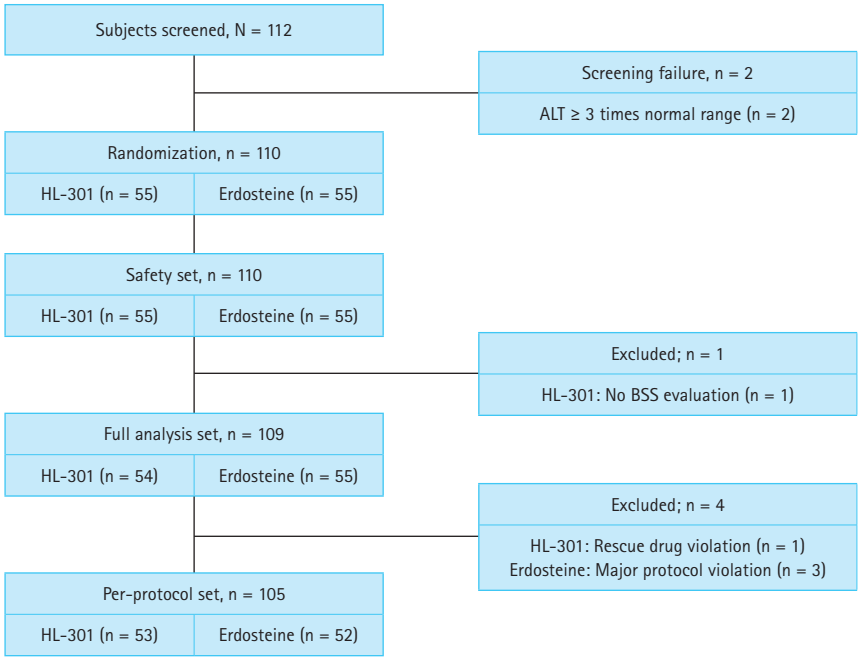

Figure 1. Flow chart showing patient enrollment. The full analysis set consisted of 54 subjects in the HL-301 group and 55 subjects in the erdosteine group. Of these, 53 subjects in the HL-301 group and 52 subjects in the erdosteine group completed the study. ALT, alanine aminotransferase; BSS, Bronchitis Severity Score.

ticipants randomly assigned to the treatment groups. The safety set included all 110 participants (55 in the HL-301 group and 55 in the erdosteine group). The FAS comprised 109 participants (54 in the HL-301 group and 55 in the erdosteine group) after excluding one participant from the HL-301 group who could not provide data for the primary efficacy endpoint (change in total BSS). The PPS included 105 participants (53 in the HL-301 group and 52 in the erdosteine group) after excluding one participant who used rescue medication within 24 hours before the final visit and three participants who significantly violated the study protocol.

Baseline characteristics

In the HL-301 group, 14.5% of the participants were male,

Table 1. Demographics and other baseline characteristics

Characteristics	HL-301 (n = 55)	Erdosteine (n = 55)	*p* value
Males	8 (14.5)	16 (29.1)	0.065[a]
Age (yr)	41.87 ± 12.99	39.16 ± 11.22	0.228[b]
Height (cm)	162.20 ± 8.17*	166.05 ± 8.61	0.013[b]
Weight (kg)	59.95 ± 12.80*	67.43 ± 17.47	0.022[b]
BMI (kg/m^2)	22.64 ± 3.40	24.18 ± 4.64	0.107[b]
Fertility	38 (69.1)	34 (61.8)	0.429[a]
Current smoker	0 (0)	0 (0)	-
β-hCG, positive	0 (0)	0 (0)	-
Chest X-ray			-
Normal	55 (100.0)	53 (96.4)	
Abnormal, not clinically significant	0 (0)	2 (3.6)	
Abnormal, clinically significant	0 (0)	0 (0)	
Medical history	24 (43.6) [55]	24 (43.6) [44]	> 0.999[a]
Bronchitis	4 (7.3)	6 (13.6)	0.516[c]
Hypertension	5 (9.1)	4 (9.1)	> 0.999[c]
Hyperlipidemia	2 (3.6)	5 (11.4)	0.252[c]

Data are expressed as mean ± standard deviation or number of subjects (%) [number of events].
BMI, body mass index; β-hCG, β-human chorionic gonadotropin.
[a]Chi-square test. [b]Wilcoxon rank sum test. [c]Fisher's exact test.
*$p < 0.05$ compared with erdosteine.

Table 2. Change in BSS from baseline

Parameter	HL-301	Erdosteine	*p* value
Per protocol set			
No. of patients	53	52	
Baseline (score)	5.74 ± 1.00	5.87 ± 1.01	0.432[a]
Day 7 (score)	1.30 ± 1.32	1.54 ± 1.45	0.392[a]
Change	-4.43 ± 1.50	-4.33 ± 1.58	
p value (within group)	< 0.001[b]	< 0.001[c]	
Difference (95% CI) (between group)	0.11 (-0.42, 0.64)		0.826[a]
Difference of LSM (95% CI) (between group)	0.20 (-0.33, 0.73)		0.454[d]

Data are expressed as mean ± standard deviation.
BSS, Bronchitis Severity Score; CI, confidence interval; LSM, least squares mean.
[a]Wilcoxon rank sum test. [b]Paired t-test. [c]Wilcoxon signed rank test. [d]ANCOVA model with baseline value as covariate.

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and the mean age was 41.87 ± 12.99 years (Table 1). In the erdosteine group, 29.1% of the participants were male, and the mean age was 39.16 ± 11.22 years. The differences in age and sex distribution between the two groups were not significant. Significant differences in height and weight were observed between the groups, but there was no significant difference in body mass index.

Adherence for the investigational drug (HL-301 or placebo) was 95.37%, and that for the control drug (erdosteine or placebo) was 92.52%, and the difference was not significant ($p = 0.4762$).

Primary efficacy endpoint: change in total BSS

In the PPS, the mean total BSS in the HL-301 group decreased significantly from 5.74 ± 1.00 at baseline to 1.30 ± 1.32 on day 7, with a mean change of -4.43 ± 1.50 ($p < 0.001$) (Table 2). In the erdosteine group, the mean total BSS decreased from 5.87 ± 1.01 at baseline to 1.54 ± 1.45 on day 7, with a mean change of -4.33 ± 1.58 ($p < 0.001$). The mean difference in BSS change between the erdosteine group and the HL-301 group was 0.11, which was not significant ($p = 0.826$) (Fig. 2). The lower limit of the one-sided 97.5% CI was -0.42, which exceeded the clinical non-inferiority margin of -0.99, indicating that HL-301 was not inferior to erdosteine in terms of total BSS change.

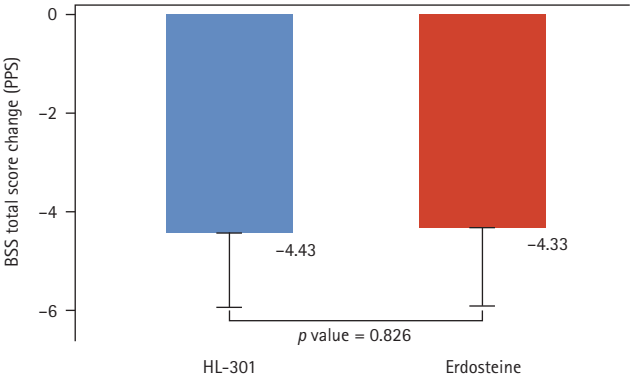

Figure 2. Total change in BSS (PPS). BSS, Bronchitis Severity Score; PPS, per protocol set.

In the FAS, the mean difference in total BSS change between the erdosteine group and the HL-301 group was 0.12, which was again not a significant difference (95% CI: -0.40, 0.63; $p = 0.773$, Supplementary Table 1, Supplementary Fig. 1). The lower limit of the one-sided 97.5% CI was -0.40, which also exceeded the clinical non-inferiority margin of -0.99, confirming non-inferiority in the FAS.

Secondary efficacy endpoints: change in BSS by symptom

In the PPS, the mean changes in BSS for individual symptoms (cough, sputum, dyspnea, chest pain during coughing, and wheezing/rhonchi) did not differ significantly between the HL-301 and erdosteine groups (Table 3, Fig. 3). Likewise in the FAS, the mean changes in BSS for each symptom from baseline to day 7 did not differ significantly between the groups (Supplementary Table 2, Supplementary Fig. 2).

Secondary efficacy endpoints: overall improvement

In the PPS, the HL-301 and erdosteine groups did not differ significantly in their overall clinical response or participant satisfaction on day 7. The investigator rated 30.19% and 47.17% of the HL-301 group as completely recovered and

Table 3. Change in BSS from baseline by symptom

Symptoms	HL-301 (n = 54)			Erdosteine (n = 55)			*p* value[a]
	Baseline	Day 7	Change	Baseline	Day 7	Change	
Per protocol set							
Cough	3.68 ± 0.64	1.70 ± 0.80	-1.98 ± 0.95*	3.56 ± 0.75	1.73 ± 0.74	-1.83 ± 0.92*	0.394
Sputum	3.09 ± 0.63	1.55 ± 0.72	-1.55 ± 0.91*	3.31 ± 0.61	1.63 ± 0.71	-1.67 ± 0.86*	0.576
Dyspnea	1.43 ± 0.60	1.04 ± 0.19	-0.40 ± 0.57*	1.42 ± 0.54	1.08 ± 0.27	-0.35 ± 0.48*	0.790
Chest pain on coughing	1.47 ± 0.61	1.02 ± 0.14	-0.45 ± 0.57*	1.54 ± 0.64	1.10 ± 0.30	-0.44 ± 0.57*	0.917
Rales on auscultation	1.06 ± 0.23	1.00 ± 0.00	-0.06 ± 0.23	1.04 ± 0.19	1.00 ± 0.00	-0.04 ± 0.19	0.670

Data are expressed as mean ± standard deviation.
BSS, Bronchitis Severity Score.
[a]Wilcoxon rank sum test.
*$p < 0.05$; Change from baseline in group.

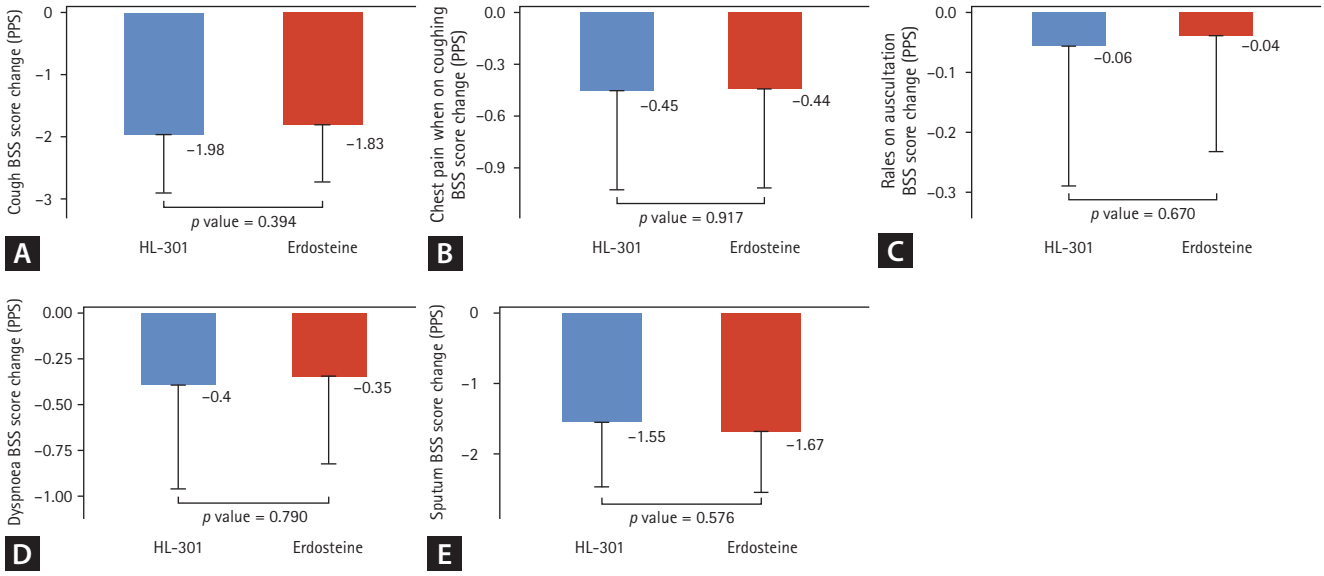

Figure 3. Change in BSS by symptom (PPS): (A) Cough and BSS change, (B) Chest pain on coughing and BSS change, (C) Rales on auscultation and BSS change, (D) Dyspnea and BSS change, (E) Sputum and BSS change. BSS, Bronchitis Severity Score; PPS, per protocol set.

Table 4. Change in inflammatory markers from baseline

Variable	HL-301 (n = 54)			Erdosteine (n = 55)			*p* value[a)]
	Baseline	Day 7	Change	Baseline	Day 7	Change	
Per protocol set							
CRP (mg/L)	0.66 ± 0.97	0.91 ± 2.31	0.26 ± 2.22	1.72 ± 4.29	1.42 ± 2.76	-0.30 ± 2.34*	0.052
TNF-α (pg/mL)	2.29 ± 6.78	1.82 ± 3.96	-0.47 ± 6.74	2.16 ± 4.85	1.23 ± 4.33	-0.93 ± 6.72*	0.138
IL-1β (pg/mL)	0.19 ± 0.71	0.07 ± 0.13	-0.12 ± 0.69	0.13 ± 0.26	0.06 ± 0.19	-0.07 ± 0.31*	0.162
IL-6 (pg/mL)	4.31 ± 15.34	2.16 ± 6.42	-2.14 ± 13.86	2.07 ± 3.07	1.59 ± 1.75	-0.48 ± 3.08	0.656

Data are expressed as mean ± standard deviation.
CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL, interleukin.
[a)]Wilcoxon rank sum test.
*$p < 0.05$; Change from baseline in group.

significantly improved, respectively, compared with 30.77% and 38.46% in the erdosteine group ($p = 0.638$). In the HL-301 group, 28.30% and 39.62% of participants were very satisfied and satisfied with treatment, respectively, compared with 30.77% and 40.38% in the erdosteine group ($p = 0.979$). These findings were consistent in the FAS, with no significant difference in overall clinical response ($p = 0.621$).

Secondary efficacy endpoints: rescue drug

In the PPS, the percentage of participants in the HL-301 group who used rescue medication was 3.77% (2/53), and the average number of doses used by the end of the study was 3.00 ± 0.00; those numbers were 7.69% (4/52) and 4.00 ± 2.94 in the erdosteine group, and the differences between the groups were not significant ($p > 0.999$). Likewise in the FAS, the groups did not differ significantly in their use of rescue medication or the total number of doses used by the end of the study ($p > 0.999$).

Secondary efficacy endpoints: inflammatory markers

In the PPS analysis, the mean changes in inflammatory markers from baseline to day 7 showed no significant decrease in CRP, TNF-α, or IL-1β level in the HL-301 group, whereas those levels did decrease significantly in the erdosteine group; however, the overall changes did not differ significantly between the groups (Table 4). Additionally, when the analysis was adjusted for baseline CRP level, the difference

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Table 5. Adverse events

Adverse events	HL-301 (n = 55)	Erdosteine (n = 55)	*p* value
Any adverse event	2 (3.6) [4]	1 (1.8) [1]	> 0.999[a]
Gastrointestinal disorder	1 (1.8) [2]	1 (1.8) [1]	
Dry mouth	-	1 (1.8) [1]	
Gastritis	1 (1.8) [1]	-	
Tooth impaction	1 (1.8) [1]	-	
Infections and infestations	1 (1.8) [1]	-	
Periodontitis	1 (1.8) [1]	-	
Investigations	1 (1.8) [1]	-	
Blood cholesterol increased	1 (1.8) [1]	-	
Serious adverse events	0 (0) [0]	0 (0) [0]	-

Data are expressed as number of subjects (percentage of subjects) [number of events].
[a]Fisher's exact test.

in CRP between the groups on day 7 was not significant (p = 0.799). IL-6 level showed no significant decrease in either group, with no significant difference in overall change between the groups. Likewise in the FAS, the mean changes in inflammatory markers did not differ significantly between the groups (Supplementary Table 3).

Safety and adverse events

Adverse events occurred in 3.6% of the participants in the HL-301 group and 1.8% in the erdosteine group, and all events were of mild severity (Table 5). The most frequently reported adverse event was gastrointestinal disorder, occurring in 1.8% of the HL-301 group and 1.8% of the erdosteine group. No serious adverse events were reported in either group.

The groups did not differ significantly in mean changes from baseline to day 7 in laboratory tests or vital signs (data not shown). Additionally, no clinically significant changes were observed in the clinical laboratory tests or physical examinations (data not shown).

DISCUSSION

This study compared the efficacy and safety of HL-301 with that of erdosteine in patients with acute bronchitis. In both the PPS and FAS analyses, HL-301 showed a reduction in total BSS on day 7 similar to that of erdosteine, with the results exceeding the non-inferiority margin of -0.99 and demonstrating that HL-301 is not inferior to erdosteine. The mean changes in BSS for each symptom (cough, sputum production, dyspnea, chest pain during coughing, and wheezing/rhonchi) were also similar between the HL-301 and erdosteine groups, with no significant differences. The safety analysis revealed that both HL-301 and erdosteine had mild adverse events with no significant differences, indicating that HL-301 is as safe as erdosteine. These findings suggest that HL-301 is as effective and safe as erdosteine in controlling individual symptoms and providing overall relief for patients with acute bronchitis.

Acute bronchitis is triggered by inflammation of the bronchial mucosa, and elevated CRP levels have been associated with an increased risk of pneumonia, indicating it as a key inflammatory marker [3]. Previous studies on botanical drugs have shown that they can suppress airway inflammation in chronic obstructive pulmonary disease (COPD) mouse models [12], and follow-up studies have observed that they can prevent TNF-α-induced inflammation in bronchial epithelial cells [13]. Additionally, a 12-week study of Synatura® (a botanical drug chiefly composed of ivy leaf extract) in patients with chronic bronchitis–type COPD showed non-significant improvements in inflammatory markers (CRP, IL-6, TNF-α, and IL-33) [14]. In the present study, CRP, TNF-α, IL-1β, and IL-6 levels were measured as inflammatory biomarkers to assess acute inflammatory state. Before treatment, the CRP levels in the erdosteine group were approximately 2.5 times higher than those in the HL-301 group, indicating a higher level of acute infection or inflammation in the erdosteine group. Although that pre-treatment difference complicated direct comparisons, no significant differences in changes in

inflammatory biomarkers were found between the HL-301 and erdosteine groups after seven days of treatment when baseline CRP level was controlled.

The findings of this study are consistent with previous research, which also demonstrated non-inferiority to Umckamin [8]. The comparable results in outcomes between HL-301 and erdosteine reinforce that HL-301 can be an effective alternative for managing acute bronchitis symptoms. This supports the idea that herbal-based treatments, such as HL-301, can offer therapeutic effects similar to synthetic drugs, potentially broadening the range of treatment options available to clinicians.

Erdosteine is commonly associated with adverse reactions such as heartburn, diarrhea, taste disturbances, nausea, abdominal pain, vomiting, eczema, and erythema [15,16]. In the HL-301 phase 3 clinical trial (HL_HL301_301), adverse events were observed in 7 of 123 participants and included gastrointestinal symptoms, skin disorders, cardiac palpitation, and increased hepatic enzyme levels [8]. In the present study, adverse events in the HL-301 group included gastrointestinal disorders (gastritis, tooth impaction), periodontitis, and increased blood cholesterol, while the erdosteine group experienced one case of gastrointestinal disorder (dry mouth). No participants discontinued treatment due to adverse events. While the incidence of adverse events in the HL-301 group was numerically higher than in the erdosteine group, these differences were not statistically significant. However, the observation that mild adverse events occurred more frequently in the HL-301 group is noteworthy. Given the limited sample size, this finding suggests that caution should be exercised when interpreting the safety profile and that future studies with larger sample sizes are warranted to validate these results.

Natural medicines available for treatment of acute bronchitis include ivy leaf extract and *Pelargonium sidoides* extract [13,14,17-23]. *P. sidoides*, an herbal medicine extracted from plant roots, has antibacterial and antiviral properties [19,22,23]. Previous studies comparing synthetic drugs with herbal medicines have focused on children aged 6–12 years and compared acetylcysteine with *P. sidoides* for seven days [17]. However, evidence for treating adult acute bronchitis with herbal medicines is lacking, and long-term studies on various treatment methods are scarce. Most existing studies compare herbal medicines with placebo, evaluating improvements in symptoms such as cough, asthma, and seizures [17,18,20,21]. In contrast, the present study demonstrated the non-inferiority of HL-301 to the synthetic drug erdosteine, supporting its efficacy in symptom relief.

Recent studies comparing combined herbal medicines with placebo have observed patients for up to 10 days, assessing not only bronchitis symptoms, but also quality of life [13,18,24]. Although this present study confirmed symptom improvement after seven days without follow-up, it is necessary to monitor the progress of acute infection–related cough and sputum, which can last for up to three weeks, through chest X-rays and physical examinations. Additionally, evaluating improvements in quality of life would be beneficial.

In this study, there were several limitations. First, there may be a limitation in generalizability as we included only patients who visited tertiary or general hospitals in South Korea. Validation is needed for patients with milder disease who visit primary care hospitals, as well as for those residing in other countries or of different races. Second, since HL-301 is a combination of seven herbs, it is difficult to determine which specific ingredients contribute to its efficacy in alleviating acute bronchitis. Third, although acute bronchitis is highly prevalent in children, we included only adult patients in this study.

In conclusion, this study demonstrated that HL-301 is as effective and safe as erdosteine for treatment of acute bronchitis. HL-301 showed reductions in total BSS and individual symptom scores similar to those of erdosteine. Safety analysis revealed mild adverse events in both groups, with no significant differences, indicating that HL-301 is a safe alternative to erdosteine. Moreover, higher medication adherence and the convenient dosing regimen of HL-301 further support its use in clinical practice. Given similar efficacy and safety profiles, along with potential advantages in patient compliance and cost-effectiveness, HL-301 presents a viable option for management of acute bronchitis. Future studies should focus on long-term outcomes and quality of life assessments to further validate these findings.

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KEY MESSAGE

1. HL-301 (300 mg twice daily) demonstrated non-inferiority to erdosteine (300 mg three times daily) in reducing the Bronchitis Severity Score (BSS) in patients with acute bronchitis after seven days of treatment.
2. Both HL-301 and erdosteine significantly reduced symptoms (cough, sputum production, dyspnea, chest pain during coughing, and wheezing), and there were no significant differences between the groups.
3. Patient satisfaction was high for both HL-301 and erdosteine, with no significant differences in the levels of satisfaction or overall clinical improvement between the groups.
4. The safety profiles of HL-301 and erdosteine were comparable, with both medications exhibiting mild adverse events and no significant differences in laboratory test results or changes in vital signs.
5. Changes in inflammatory markers (CRP, TNF-α, IL-1β, and IL-6) were similar between the groups, indicating comparable anti-inflammatory effects.

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Correspondence to:
Kwang Ha Yoo, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1, Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea
Tel: +82-2-2030-7522, Fax: +82-2-2030-7018
E-mail: 20010025@kuh.ac.kr
https://orcid.org/0000-0001-9969-2657

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CRedit authorship contributions
Ji-Yong Moon: conceptualization, resources, investigation, data curation, writing - original draft, writing - review & editing; Joon Young Choi: investigation, writing - original draft, writing - review & editing; Youlim Kim: investigation, project administration; Hye Jung Park: investigation, writing - review & editing, project administration; Yong Bum Park: investigation, writing - review & editing, project administration; Seong Yong Lim: investigation, writing - review & editing, project administration; Kyung Hoon Min: resources, investigation, writing - review & editing, project administration; Deog Kyeom Kim: methodology, resources, investigation, writing - review & editing, project administration; Chin Kook Rhee: methodology, resources, investigation, writing - review & editing, supervision, project administration; Seung Won Ra: resources, investigation, writing - review & editing, project administration; Chang Youl Lee: methodology, resources, writing - review & editing, project administration; Yong Il Hwang: methodology, resources, writing - review & editing, project administration; Kwang Ha Yoo: conceptualization, methodology, resources, investigation, writing - review & editing, supervision, project administration, funding acquisition

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