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Original Article

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Advanced clinical symptoms of the antihangover compound HK-GCM-H01 in healthy Koreans

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ABSTRACT

A hangover is a combination of negative mental and physical symptoms, such as headache, diarrhea, and loss of appetite, that occur after alcohol consumption and can vary depending on individual genetic and environmental factors. To quickly relieve these hangover symptoms, a new hangover relief compound called HK-GCM-H01 has been developed. This compound, HK-GCM-H01, consists of fermented rice germ extracts, yeast extract mixtures, cili extract powder, and concentrated nipafam powder, all of which are known to relieve hangover symptoms. The safety and clinical symptoms of HK-GCM-H01 were evaluated, along with the pharmacokinetic properties of alcohol and acetaldehyde after its administration. This study was conducted on 50 healthy Korean men using a randomized, double-blind, placebo-controlled, single-intake, crossover design. To evaluate clinical symptoms, Acute Hangover Scale and Alcohol Hangover Severity Scale were used, and the pharmacokinetic evaluation parameters included the maximum plasma concentration, the time to peak plasma concentration, the terminal half-life, and the area under the plasma concentration-time curve from X hours to Y hours. A significant reduction in clinical symptoms was observed after alcohol consumption in the group that consumed HK-GCM-H01 with added hangover relief compound, as was a significant decrease in blood exposure to acetaldehyde compared to the placebo group. There were no adverse events or significant changes in liver function indicators reported during the safety evaluation. These findings indicate that HK-GCM-H01 is safe and significantly reduces plasma concentrations of acetaldehyde, the main cause of hangover, suggesting that it improves hangover symptoms.

Keywords: Alcohol Drinking; Acetaldehyde; Ethanol; Pharmacodynamics; Pharmacokinetics

INTRODUCTION

Hangovers are defined as the combination of negative mental and physical symptoms that can be experienced after a single episode of alcohol consumption with the potential to significantly impact an individual's daily life and work performance [1]. Typical hangover symptoms include headache, diarrhea, loss of appetite, nausea, vomiting, chills, and cold sweats, which can also manifest as cognitive impairment, impaired motor skills, hematological changes, and hormonal fluctuations [2]. Hangovers typically commence when plasma alcohol levels approach zero following a single episode of alcohol consumption [3].

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Toxicity from the metabolites, such as acetaldehyde, formaldehyde, and acetone, generated during alcohol breakdown and the accumulation of acetaldehyde, along with nutritional imbalances, are closely associated with hangover symptoms [4,5]. Specifically, acetaldehyde promotes the generation of radicals that contribute to cellular damage, negatively impacting the nervous and immune systems and exacerbating hangover symptoms [6]. Nutritional imbalances, another cause of hangovers, result from the dysregulated absorption and breakdown of proteins, fats, vitamins, and minerals due to dehydration-induced deficiencies within the body [7]. However, hangovers do not affect everyone uniformly and may vary among individuals due to genetic predispositions, nutritional status, physical activity levels, degree of dehydration, and overall health conditions, resulting in differences in the severity and manifestation of symptoms [8].

In recent years, the popularity of hangover relief products and supplements has increased, with many individuals using these products to quickly alleviate hangover symptoms and return to their normal daily activities. Common ingredients in existing hangover relief beverages include fermented rice germ extracts and *Hovenia dulcis* Thunb. extracts, which have been reported to aid in hangover relief. Fermented rice germ extracts are natural extracts obtained by fermenting rice embryos and soybeans and are rich in vitamins and minerals that help remove bad breath and promote the breakdown of alcohol. Moreover, the absorption rate of the vitamins and minerals contained in fermented rice germ extracts can be enhanced by the fermentation process [9]. Additionally, fermented rice germ extracts have been shown to protect the gastric mucosa and have antioxidant effects against alcohol [10]. *H. dulcis* Thunb. extracts have been shown in previous studies to potentially aid in hangover relief, as evidenced by the lower concentrations of alcohol and acetaldehyde in the *H. dulcis* Thunb. groups than those in the nontreated control groups. However, there was no difference in the activities of the alcohol-metabolizing enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) [11]. Additionally, in another study of prolonged alcohol administration, extracts of *H. dulcis* Thunb. inhibited liver damage and the development of fatty liver [12].

Effective hangover relief requires supplementation with antioxidant compounds that promote alcohol metabolism to reduce the accumulation of alcohol metabolites such as acetaldehyde, a major contributor to the pathological symptoms, and protect cells from damage caused by the radicals generated during alcohol metabolism. Fermented rice germ extracts, which are common ingredients in existing hangover relief beverages, have been shown in previous studies to have hangover-relieving effects by promoting alcohol metabolism and acting as an antioxidant. Yeast extract mixtures are known to promote alcohol metabolism by facilitating the breakdown of alcohol into acetaldehyde and promoting the excretion of some alcohol out of the cell, thereby aiding alcohol metabolism [13]. Cili extract powder, a natural extract powder that enhances the activity of ADH, ALDH, and superoxide dismutase, has been shown to reduce the concentrations of alcohol and acetaldehyde in the blood [14]. Concentrated nipafam powder contains abundant phenolic acids and flavonoids, which provide antioxidant and anti-inflammatory effects and are believed to contribute to hangover relief [15,16]. Considering the efficacy of these four ingredients, it is anticipated that a synergistic effect will be observed when they are used together. Therefore, to enhance the efficacy of existing hangover relief beverages, a new hangover relief compound composed of fermented rice germ extracts, yeast extract mixtures, cili extract powder, and concentrated nipafam powder was developed.

The investigational product (IP) was designed using HK-GCM-H01, which includes the active ingredients of the hangover relief compound, and a placebo, without the hangover relief compound. The same ingredients were included in the placebo and HK-GCM-H01 with the exception of the active hangover relief ingredients, and both the placebo and HK-GCM-H01 were manufactured to have an identical aroma, taste, and color. Additionally, labels were attached to the entire containers of all IPs to prevent the contents from being visible, ensuring double blinding. In this study, we aimed to scientifically determine whether a hangover relief compound containing fermented rice germ extracts, yeast extract mixtures, cili extract powder, and concentrated nipafam powder could effectively alleviate the hangover symptoms caused by alcohol in 50 healthy adults. We also aimed to evaluate the safety and clinical symptoms of this hangover relief compound, along with the pharmacokinetics (PK) of ethyl alcohol and acetaldehyde.

METHODS

Subjects

This study received approval from the Institutional Review Board (IRB) of Chungbuk National University Hospitaland was not subject to investigational new drug approval because it did not involve investigational drugs (IRB No. 2023-09-021). All procedures were conducted in accordance with the International Conference on Harmonization-Good Clinical Practice guidelines and the Helsinki Declaration, and written consent was obtained from all participants before study-related procedures were initiated.

Healthy Korean subjects aged between 20 and 40 years with a body mass index (BMI) between 18.0 kg/m^2 and 25.0 kg/m^2 were selected. The selection criteria included a history of past hangover experiences and regular alcohol consumption of at least once a month, with a typical amount of one or more bottles of soju (16.5% alcohol by volume) per drinking session. However, participants with clinically significant medical histories that could affect their safety or the PK of HK-GCM-H01 were excluded, as were pregnant or lactating women.

Study design

This study was a randomized, double-blind, placebo-controlled, single-intake, crossover trial. The 50 subjects were randomized into two groups of 25 each with different intake sequences, and the washout period between sequences was 8 days (**Fig. 1**).

The IP was administered 2 hours after a regular meal, followed by the intake of either HK-GCM-H01 or Placebo according to the sequence. Thirty minutes after ingestion, the individual subjects consumed alcohol within 15 minutes in an amount adjusted based on

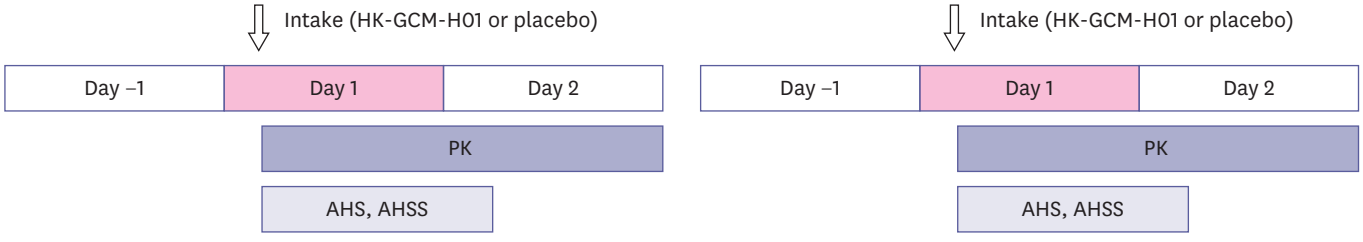

Figure 1. Study design.
PK, pharmacokinetics; AHS, Acute Hangover Scale; AHSS, Alcohol Hangover Severity Scale.

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their body weight. A minimum of 4 hours after alcohol consumption, another meal was provided. During alcohol consumption, minimal snacks were allowed, and water intake was restricted for 2 hours following alcohol consumption.

The amount of alcohol provided varied based on each subject's body weight, administering 0.78 g of alcohol per 1 kg of body weight. Additionally, the type of alcohol provided to the subjects in this study was a mixture of whiskey and red wine in a ratio of 1:1 based on the amount of alcohol (g). The whiskey alcohol content was 40% while the red wine alcohol content was 19.5%.

Clinical symptoms

In this study, questionnaires were conducted to subjectively assess the severity of the hangover symptoms in subjects after alcohol consumption in the HK-GCM-H01 and Placebo groups. The Alcohol Hangover Severity Scale (AHSS) and Acute Hangover Scale (AHS) were utilized for the questionnaire. Assessments were conducted 1, 4, 8, and 15 hours after alcohol intake during each period.

Ethyl alcohol and acetaldehyde

To evaluate the PK of ethyl alcohol and acetaldehyde, blood samples were collected at baseline (0 hours, before alcohol intake) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 15 hours after alcohol intake. At each time point, 4 mL of blood was collected into two sodium fluoride/Na_2 EDTA tubes, each tube containing 2 mL. The samples were then centrifuged at 3,000 rpm for 10 minutes at 4°C. After centrifugation, the plasma was mixed with thiourea solution and the standard substance *tert*-butanol in sequence and stored in a headspace vial at −85°C to −65°C until analysis.

Ethyl alcohol and acetaldehyde concentrations were measured using headspace gas chromatography/tandem mass spectrometry and analyzed using a Quantitative Analysis 12.0 instrument (Agilent Technologies, Inc., Santa Clara, CA, USA). The lower limit of quantification (LLOQ) was 20 μg/mL for ethyl alcohol and 0.2 μg/mL for acetaldehyde. The accuracy and precision within the assay were set to within 100.0 ± 15.0% of the mean concentration of the first obtained concentration for each assay and ≤ 15.0%, respectively. The accuracy and precision between assays were set to within 100.0 ± 15.0% of the mean concentration of the three repeated measurements for each assay and ≤ 15.0%, respectively. For the LLOQ, the accuracy was set to within 100.0 ± 20.0%, and the precision was set to ≤ 20.0% for both the inter- and intraassay conditions. Stability was considered acceptable if the accuracy of the mean concentration determined with the stability samples processed under each condition was within 100.0 ± 15.0% and the precision was ≤ 15.0%.

The PK parameters for ethyl alcohol and acetaldehyde were determined using Phoenix WinNonlin® version 8.3 (Certara, NJ, USA) and included the maximum plasma concentration and the time to peak plasma concentration (T_{max}). The terminal half-life ($t_{1/2}$) was calculated from the slope obtained by linear regression analysis of the log-linear plot corresponding to the terminal phase of the plasma concentration-time curve using the elimination rate constant (λ_Z) and $\ln(2)/\lambda_Z$. The area under the plasma concentration-time curve from X hours to Y hours was calculated using the linear trapezoidal method with linear interpolation.

For acetaldehyde, which may be influenced by the intake of food in addition to the amount of alcohol consumed [17], analysis was performed using values adjusted for baseline

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concentrations, with the baseline value for each time point corrected based on the predose. Pharmacokinetic parameters were calculated using the baseline-corrected values (subtracting the baseline), and any negative values were set to "0".

Safety evaluation

Safety evaluations included assessments of adverse events (AEs), concomitant medication (CM), vital signs, physical examination, 12-lead electrocardiogram, and clinical laboratory examinations. The severity of AEs was classified as mild, moderate, or severe, and the causal relationship between the AE and IP was also evaluated.

To monitor safety, changes in liver function indicators after alcohol intake were compared to the baseline parameters. The liver function indicators included alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (γ-GT). Blood samples for measuring liver function indicators were collected before alcohol intake (predose) and 15 hours after alcohol intake and analyzed at the Department of Laboratory Medicine, Chungbuk National University Hospital.

Statistical analysis

Statistical analysis was performed using SAS® Analytics Pro version 9.4 (SAS Institute Inc., Cary, NC, USA), with the significance level set at 5%. For the PK analysis of ethyl alcohol and acetaldehyde, Phoenix WinNonlin® version 8.3 was used to calculate the descriptive statistics for the PK parameters and conduct intergroup comparisons. Demographic information and safety evaluations were analyzed using two-sample *t*-tests or Wilcoxon rank-sum tests, while medical history and physical examination data were analyzed using Fisher's exact test. To evaluate the questionnaire responses at each time point, a linear mixed-effect model was applied, and for the pharmacokinetic parameters, the two-sample *t*-test or Wilcoxon rank-sum test was used for analysis. AEs were standardized and compared using the Medical Dictionary for Regulatory Activities (MedDRA®, version 26.1; Herndon, VA, USA).

RESULTS

Demographics

A total of 50 subjects were enrolled, and all registered subjects consumed the IP at least once. Subsequently, 7 subjects withdrew voluntarily for personal reasons, resulting in 43 subjects completing the entire study. Demographic analysis was conducted on all 50 subjects who were assigned subject numbers.

All subjects were male, with mean (± standard deviation) values for age, weight, and BMI were 26.96 ± 4.54 years, 70.18 ± 5.74 kg, and 22.95 ± 1.32 kg/m^2, respectively, and there were no significant differences between the treatment groups (**Table 1**).

Upon examining the information on gender, smoking history, drinking history and caffeine intake, there were no statistically significant differences in distribution between the treatment groups (**Table 2**).

Clinical symptoms

Clinical symptom analysis was conducted on the 43 subjects who consumed the IP at least once and completed the entire study in the specified order.

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Table 1. Demographics characteristics of the subjects who enrolled the study

PK parameters (units)	Sequence 1 (n = 25)	Sequence 2 (n = 25)	Total (n = 50)	*p*-value
Age (yr)				0.546*
Mean ± SD	26.48 ± 4.33	27.44 ± 4.78	26.96 ± 4.54	
Range	21.00–35.00	22.00–37.00	21.00–37.00	
Height (cm)				0.611†
Mean ± SD	175.26 ± 6.36	174.38 ± 5.74	174.82 ± 6.01	
Range	164.20–190.00	165.50–186.60	164.20–190.00	
Weight (kg)				0.315†
Mean ± SD	71.00 ± 5.41	69.35 ± 6.05	70.18 ± 5.74	
Range	63.40–86.00	58.30–83.00	58.30–86.00	
BMI (kg/m^2)				0.384†
Mean ± SD	23.12 ± 1.21	22.79 ± 1.43	22.95 ± 1.32	
Range	20.90–25.00	19.50–24.80	19.50–25.00	

PK, pharmacokinetics; SD, standard deviation; BMI, body mass index.
*Wilcoxon rank-sum test; †Two-sample *t*-test.

Table 2. Demographics characteristics

PK parameters (units)	Sequence 1 (n = 25)	Sequence 2 (n = 25)	Total (n = 50)	*p*-value
Sex				-
Male	25 (100.00)	25 (100.00)	50 (100.00)	
Female	0 (0.00)	0 (0.00)	0 (0.00)	
Smoking history				0.564*
Present	16 (64.00)	14 (56.00)	30 (60.00)	
Absent	9 (36.00)	11 (44.00)	20 (40.00)	
Drinking history				-
Present	25 (100.00)	25 (100.00)	50 (100.00)	
Absent	0 (0.00)	0 (0.00)	0 (0.00)	
Caffeine intake				0.145*
Present	7 (28.00)	12 (48.00)	19 (38.00)	
Absent	18 (72.00)	13 (52.00)	31 (62.00)	

Values are presented as number (%).
PK, pharmacokinetics.
*χ^2 test.

In this study, total score of AHSS in placebo group was higher than HK-GCM-H01 group in every time points (1, 4, 8, 15 hours), but significant differences were not observed (**Fig. 2**). Significant differences were observed between HK-GCM-H01 and placebo in terms of hangover relief evaluated by AHSS confusion at 4 hours, thirst at 15 hours, and shivering at 1 hour. Additionally, significant differences were found in AHS thirst at 15 hours and dizziness/faintness at 1 hour (**Table 3**).

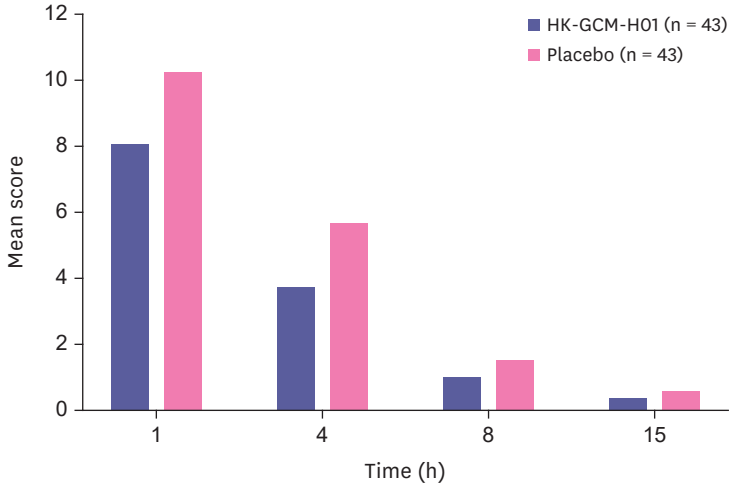

Figure 2. Total score of Alcohol Hangover Severity Scale.

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Table 3. Summary of significant differences in the AHSS and AHS

PK parameters (units)	Time (h)	HK-GCM-H01 (n = 43)	Placebo (n = 43)	95% CI*	*p*-value†
AHSS					
Confusion	4	0.09 ± 0.37	0.37 ± 0.09	(−0.50, −0.02)	0.032
Thirst	15	0.14 ± 0.41	0.02 ± 0.15	(0.00, 0.24)	0.046
Shivering	1	0.05 ± 0.30	0.23 ± 0.68	(−0.34, −0.01)	0.036
AHS					
Thirsty	15	0.14 ± 0.41	0.02 ± 0.15	(0.00, 0.24)	0.046
Dizziness/ faintness	1	0.56 ± 1.26	0.33 ± 0.81	(0.03, 0.49)	0.029
Total score‡	4	−1.88 ± 3.94	−0.23 ± 4.05	(−3.05, −0.31)	0.017

Values are represented as the arithmetic mean ± standard deviation.
AHSS, Alcohol Hangover Severity Scale; AHS, Acute Hangover Scale; PK, pharmacokinetics; CI, confidence interval.
*(Lower, upper); †Linear mixed effect model; ‡The difference between the measured values and 1 hour.

Ethyl alcohol and acetaldehyde

The absorption and elimination patterns of ethyl alcohol and acetaldehyde appeared similar, with rapid absorption after administration followed by a decrease in a zero-order elimination manner after reaching T_{max}. The T_{max} of ethyl alcohol in the two groups administered HK-GCM-H01 and placebo gave median values of 1.00 hours and 1.50 hours, respectively, after alcohol intake. The estimated $t_{1/2}$ values were similar between the HK-GCM-H01 and the placebo groups, at 1.01 ± 0.38 hours and 1.07 ± 0.47 hours, respectively, and almost all the subjects had negligible plasma ethyl alcohol levels 8 hours after alcohol administration (**Fig. 3**). For acetaldehyde, the T_{max} was the same in both the HK-GCM-H01 and placebo groups (0.50 hours), with $t_{1/2}$ values of 9.58 ± 9.99 hours and 13.16 ± 17.22 hours, respectively. Acetaldehyde concentrations were negligible in almost all subjects 10 hours after alcohol administration, and while the absorption process leading to T_{max} was similar between the HK-GCM-H01 and placebo groups, the elimination of acetaldehyde was faster with HK-GCM-H01.

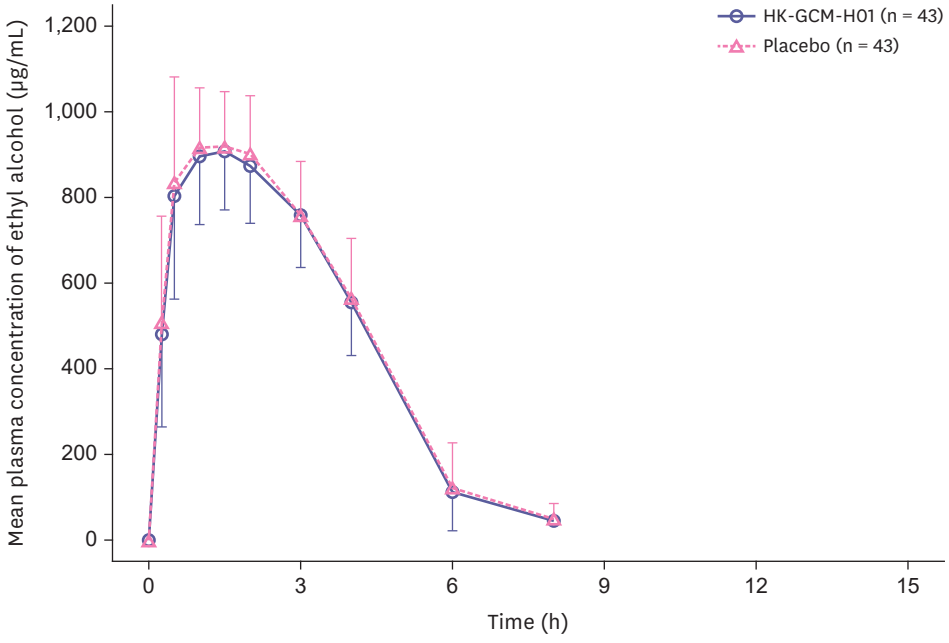

Figure 3. Mean plasma concentration of ethyl alcohol.

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The AUC_{6-12h} for acetaldehyde was 1.11 ± 0.68 h × μg/mL for HK-GCM-H01 and 1.18 ± 0.77 h × μg/mL for placebo. Among a total of 43 subjects, 15 subjects in the HK-GCM-H01 group had detectable baseline acetaldehyde levels with a mean concentration of 0.23 μg/mL, and 10 in the placebo group with a mean concentration of 0.22 μg/mL. The baseline-adjusted AUC_{6-12h} for acetaldehyde was 0.20 ± 0.38 h × μg/mL for HK-GCM-H01 and 0.39 ± 0.74 h × μg/mL for placebo, indicating lower plasma acetaldehyde exposure with HK-GCM-H01 than with placebo, with a significant *p*-value of 0.025 (**Table 4**, **Fig. 4**).

Safety and tolerability

Among all 50 subjects who consumed the IP at least once, no AEs were reported, excluding hangover symptoms, as determined through survey responses following alcohol consumption. Additionally, there were no reported instances of CM use. There were also no clinically significant findings in terms of the vital signs, physical examinations, 12-lead electrocardiograms, or clinical laboratory tests.

In particular, there were no significant differences observed in the liver function indices (ALT, AST, and γ-GT) between baseline and each postdose time point or in the percent change from baseline across the treatment groups.

DISCUSSION

In this study, the pharmacokinetic effects of the developed hangover-relieving compound were evaluated. The definition of a hangover includes the negative symptoms that can occur after alcohol consumption and can manifest in various ways depending on the individual. To assess the various degrees of hangover that may occur, standardized questionnaires, such as AHSS, AHS, and Hangover Severity Scale, were utilized [18,19]. While all three questionnaires are suitable for use in all hangover-related studies, it is appropriate to use a combination of two or more questionnaires [20]. Additionally, previous studies have traditionally utilized

Table 4. Summary of the PK parameters from plasma after a single dose of alcohol consumption

PK parameters (units)	HK-GCM-H01 (n = 43)		Placebo (n = 43)		95% CI*	*p*-value†
	Mean ± SD	CV%	Mean ± SD	CV%		
Ethyl alcohol						
C_{max} (μg/mL)	964.74 ± 167.39	17.35	980.3 ± 163.80	16.71	(−46.70, 20.36)	0.432
AUC_{0-15h} (h × μg/mL)	3,892.35 ± 745.35	19.15	4,003.59 ± 792.86	19.8	(−246.99, 27.40)	0.114
AUC_{6-12h} (h × μg/mL)	197 ± 188.54	95.71	227.52 ± 211.60	93	(−76.43, 14.84)	0.180
T_{max}‡ (h)	1.00 (0.50–3.00)		1.50 (0.50–3.00)		(−0.23, 0.19)	0.853
$t_{1/2}$ (h)	1.01 ± 0.38	38.11	1.07 ± 0.47	44.21	(−0.18, 0.05)	0.227
Acetaldehyde						
C_{max} (μg/mL)	0.64 ± 0.75	117.03	0.66 ± 0.72	108.04	(−0.12, 0.11)	0.881
AUC_{0-15h} (h × μg/mL)	3.95 ± 2.78	70.46	3.94 ± 2.76	69.9	(−0.42, 0.72)	0.593
AUC_{6-12h} (h × μg/mL)	1.11 ± 0.68	61.57	1.18 ± 0.77	65.28	(−0.27, 0.23)	0.890
T_{max}† (h)	0.50 (0.00–3.00)		0.50 (0.00–3.00)		(−0.16, 0.58)	0.259
$t_{1/2}$ (h)	9.58 ± 9.99	104.22	13.16 ± 17.22	130.83	(−10.35, 3.77)	0.356
Baseline corrected acetaldehyde						
C_{max} (μg/mL)	0.56 ± 0.76	135.67	0.61 ± 0.73	118.86	(−0.17, 0.08)	0.4878
AUC_{0-15h} (h × μg/mL)	1.93 ± 2.57	133.18	2.2 ± 2.78	126.14	(−0.66, 0.27)	0.4003
AUC_{6-12h} (h × μg/mL)	0.2 ± 0.38	189.69	0.39 ± 0.74	190.11	(−0.30, −0.02)	0.0245
T_{max}† (h)	0.50 (0.00–3.00)		0.50 (0.00–3.00)		(−0.16, 0.58)	0.2592
$t_{1/2}$ (h)	7.86 ± 11.39	145.01	11.53 ± 17.08	148.13	(−10.56, 3.98)	0.3696

PK, pharmacokinetics; SD, standard deviation; CV, coefficient of variation; CI, confidence interval; C_{max}, maximum plasma concentration; $AUC_{(X-Yh)}$, area under the plasma concentration-time curve from X hours to Y hours; T_{max}, time to peak plasma concentration; $t_{1/2}$, terminal half-life.
*(Lower, upper); †Linear mixed effect model; ‡Median (minimum–maximum).

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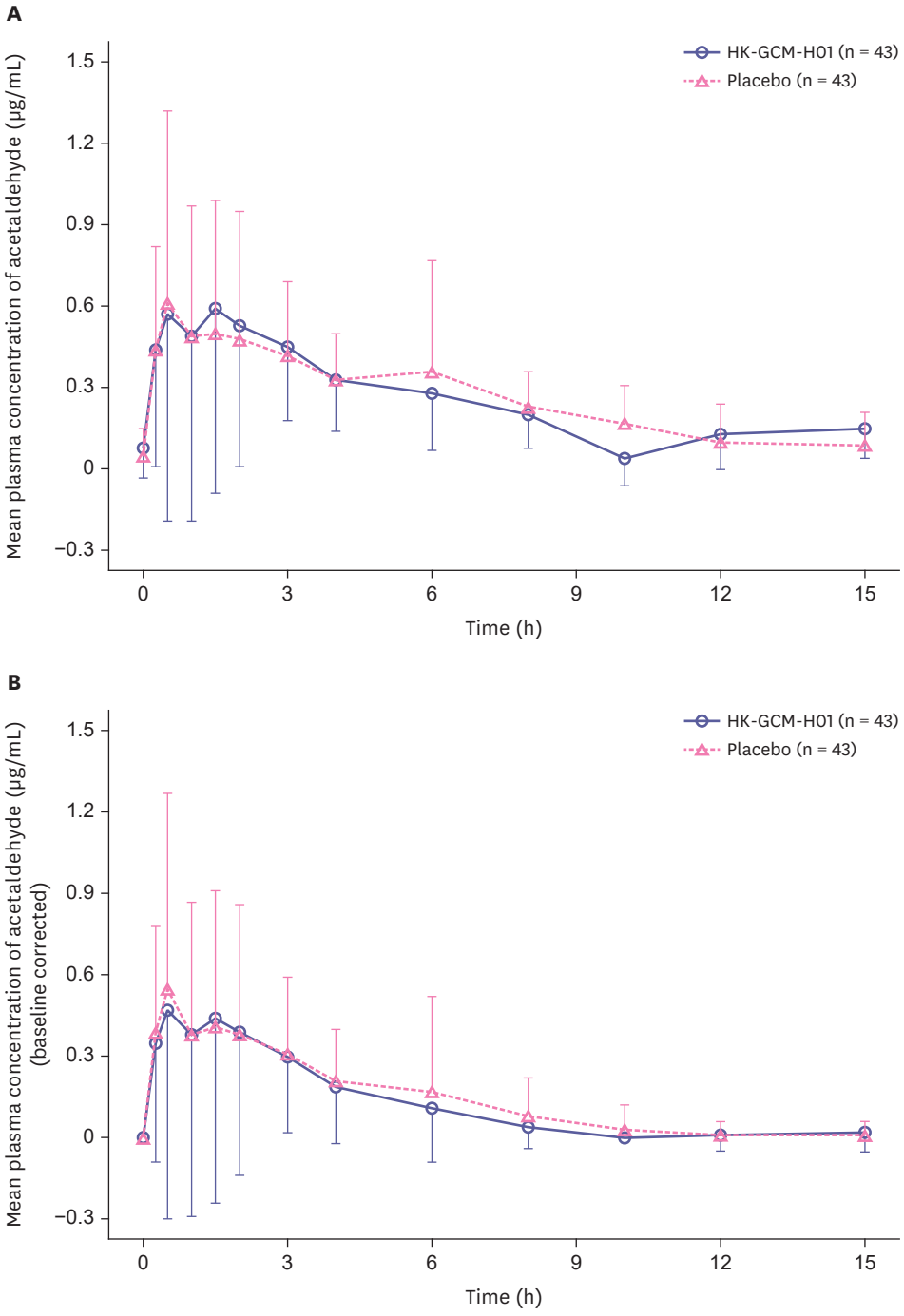

Figure 4. Mean plasma concentration of acetaldehyde. (A) Original and (B) baseline corrected.

objective indicators, such as changes in plasma ethyl alcohol, acetaldehyde, and expiratory air ethyl alcohol concentrations, of hangover symptoms [21]. In particular, acetaldehyde, a metabolite of absorbed alcohol, is known as the primary causative agent of hangover and serves as a direct biomarker for assessing hangover severity [5]. The concentrations of these indicators at various time points were used for comparison, and the evaluation criteria of this study were also set accordingly to reflect this approach.

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Fermented liquor causes more severe hangovers than distilled alcohol, mainly due to the higher content of impurities generated during the fermentation process. In the case of wine, substances such as tannins and histamines are known to induce headaches [22], and notably, red wine has been found to contain ten times more flavonols, such as quercetin, than white wine [23]. Quercetin is converted to quercetin glucuronide in the body, which inhibits ALDH2, an enzyme that converts acetaldehyde to acetate, leading to the accumulation of acetaldehyde and subsequent hangover [24]. Therefore, in this study, subjects were provided with a mixture of whiskey and red wine in a 1:1 ratio based on alcohol content (g). Additionally, individuals with a history of consuming at least one bottle of soju were selected as subjects, considering the varying capacities to metabolize ethyl alcohol and acetaldehyde due to genetic factors among individuals.

In the AHSS evaluation of confusion at the 4-hour time point and shivering at the 1-hour time point, significantly lower AHSS scores were observed in the HK-GCM-H01 group than in the placebo group, with *p*-values of 0.032 and 0.036, respectively. Additionally, for the overall AHS score, there was a greater difference between the HK-GCM-H01 and placebo groups at 4 hours than at 1 hour, with a significant *p*-value of 0.017. However, for items related to dizziness in both the AHS and AHSS questionnaires, although significant differences were observed between the HK-GCM-H01 and placebo groups, it is reasonable to attribute these findings to unexplained biases considering the discrepancies in the results for similar questions between the dizziness/faintness item in the AHS and the dizziness item in the AHSS performed at the same time and considering that these results are not associated with the pharmacokinetic characteristics of ethyl alcohol and acetaldehyde. Additionally, at the 15-hour time point, thirst was significantly different between the groups in both the AHSS and AHS evaluations. However, this symptom can be attributed to the diuretic effect and inhibition of antidiuretic hormone secretion due to alcohol intake [25] rather than the effects of HK-GCM-H01 or placebo. Therefore, considering the pharmacokinetic characteristics of ethyl alcohol (negligible concentration after 8 hours) and acetaldehyde and considering that all subjects showed normal liver function test results, no toxic reactions to alcohol, and no other clinically significant changes, it is reasonable to attribute these unexplained biases to chance events.

When assessing subjects' symptoms using a questionnaire, the AHSS at the 1-hour time point showed that the HK-GCM-H01 group had generally lower average scores than the placebo group across most items. Notably, there were differences, though not statistically significant, in typical hangover symptoms such as fatigue, apathy (lack of interest/concern), thirst, and shivering. Furthermore, the differences between the 1-hour time point and subsequent time points in the AHSS were calculated, revealing a statistically significant decrease at the 4-hour time point. This indicates that the HK-GCM-H01 group experienced a faster alleviation of subjective hangover symptoms at the 4-hour time point compared to the placebo group. These findings demonstrate the rapid anti-hangover effect of the HK-GCM-H01. Difference between AHSS score of each symptoms was observed. Among symptoms, scores in fatigue, thirst, concentration problems, clumsiness, confusion were observed to be higher than other symptoms in overall subjects, this result was similar to prior development study of AHSS [20]. Of the five highest scored symptoms, subjects who were administered HK-GCM-H01 group had lower score than placebo group at every time points, except for thirst at 8, 15 hours.

There were no clinically significant differences observed for the remaining symptoms, which can be attributed to the fact that many subjects did not report any symptoms. Among the total number of evaluations conducted via questionnaire (372 in total), there were 151

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(40.6%) in which no symptoms of hangover were reported on either the AHSS or the AHS. This indicates that it may have been challenging to conduct clear surveys and evaluations due to the cognitive impairment and lethargy resulting from alcohol consumption rather than indicating the absence of any symptoms after alcohol intake. Moreover, symptoms were reported subjectively and can be influenced by familiarity with the surrounding environment and alcohol consumption, which could introduce bias into the data interpretation. However, only two out of 43 subjects reported no hangover symptoms at any of the time points evaluated in this study, which represents a very small proportion of the total sample. Therefore, the lack of significant differences in symptoms may not be due to insufficient alcohol consumption or incorrect timing of the evaluations. Consequently, it is difficult to conclude that HK-GCM-H01 did not show efficacy compared to placebo, given the lack of significant differences in symptoms.

In the PK evaluation of ethyl alcohol and acetaldehyde, the T_{max} of acetaldehyde occurred at 0.50 hours, while that of ethyl alcohol ranged from 1.00 to 1.50 hours. The reason for the faster T_{max} of acetaldehyde, a metabolite of alcohol, is that alcohol undergoes zero-order elimination kinetics, causing the rapid saturation of ADH when consumed at appropriate doses [26]. This process is known to be heavily influenced by genetic factors, which leads to significant individual variations [8]. The onset time of hangover also varies due to a variety of factors, but it generally occurs 8 to 16 hours after alcohol consumption [27]. Hangover is defined as starting the day after alcohol consumption when the plasma ethyl alcohol concentration reaches zero [18]. The observed clearance of ethyl alcohol from the plasma in this study was observed in some subjects as early as 6 hours after alcohol consumption, with complete clearance observed in most subjects after 8 hours, showing a similar trend to previously reported findings.

In this study, the baseline-corrected $AUC_{6\text{-}12h}$ values of acetaldehyde 6 hours after alcohol consumption were significantly lower in the HK-GCM-H01 group (0.20 ± 2.57 h × μg/mL) than in the placebo group (0.39 ± 0.74 h × μg/mL). Additionally, although the baseline-corrected AUC values of acetaldehyde at each time point were not significantly different, HK-GCM-H01 had lower values than the placebo. This suggests that the reduced exposure to acetaldehyde during the period when a hangover typically occurs could lead to a decrease in hangover symptoms. The significantly lower values observed for acetaldehyde exposure during the 6- to 12-hour period after HK-GCM-H01 consumption when hangover is expected to occur suggest that the ingestion of HK-GCM-H01 may help reduce hangover symptoms. This result is a significant factor that can explain the differences in hangover symptoms between the test drug and the control drug at 8 hours and 15 hours.

Some limitations of this study that can be inferred from the results are as follows. First, biological factors, including brain function and sex hormone levels, may influence the differences in PK associated with alcohol consumption, especially considering sex differences [28]. However, all participants in this study were healthy Korean males aged between 20 and 40 years. To extrapolate the results of this study to the general population, additional studies involving individuals with diverse demographics may be necessary. Second, hangover symptoms are subjective and can vary among individuals, so the amount of alcohol used in this study may not have been sufficient. However, it should be noted that only 2 subjects did not report any hangover symptoms in this study. Administering larger amounts of alcohol could lead to moderate or severe adverse reactions or liver toxicity in individuals, highlighting the importance of careful consideration when setting the alcohol dose. Third, alcohol is

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lipophilic, so differences in the volume distribution based on body fat may exist. While BMI was considered to address this concern, additional tests, such as bioelectrical impedance analysis, may be needed for further verification.

From a safety perspective, the absence of reported AEs and the lack of clinically significant findings observed in this study indicate that the developed hangover relief compound is safe. Furthermore, from the questionnaires, the improved efficacy of the hangover relief compound supplemented with HK-GCM-H01 compared to the placebo was confirmed, which was also evidenced by the PK evaluation of ethyl alcohol and acetaldehyde, which revealed lower exposure to acetaldehyde after HK-GCM-H01 ingestion. Therefore, based on the data from this study, the hangover-alleviating formulation is safe and effective in improving hangover symptoms.

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