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Effects of a Health Drink Containing the Extract of the *Hovenia Dulcis* Fruit Stalk and Theracurmin, on Ethanol-Induced Hangover

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Abstract

The fruit stalk of *Hovenia dulcis (H.dulcis)* is traditionally used to relieve hangovers in Korea. Theracurmin is a highly absorbable curcumin preparation which increases the bioavailability of curcumin. Curcumin is known for its antioxidant and anti-inflammatory effects. However, the role of this combination in lowering alcohol levels in the body, thereby alleviating the severity of alcohol-induced hangover has not been investigated. Therefore, we conducted a study to investigate the eliminatory effects of a health drink containing the extract of the *H. dulcis* fruit stalk and theracurmin (theracurmin drink) on ethanol-induced hangover in rats. The theracurmin drink delivered orally to rats 30 mins before the administration of 40% ethanol (5 g/kg body weight), lowered the concentration of ethanol and acetaldehyde in the blood samples collected 1, 3, and 5 h after ethanol administration. Furthermore, the theracurmin drink increased the activities of alcohol dehydrogenase and aldehyde dehydrogenase enzymes. The effectiveness of the theracurmin drink was thus superior to that of other health drink products, suggesting that its consumption may alleviate or prevent an alcohol-induced hangover.

Key Words : *Hovenia dulcis*, alcohol, hangover, theracurmin

I. Introduction

Alcohol consumption is a major public health issue due to alcohol-related diseases and addiction. Alcohol-related diseases include malignant tumors of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and breast (Seitz & Stickel 2007). In addition, there are significant socioeconomic losses related to alcohol hangover, for example, alcohol-related absenteeism, and injuries and illnesses (Foster & Vaughan 2005; Piasecki et al. 2005; Prat et al. 2008). In south Korea, the social cost of drinking alcohol announced in 2013 was KRW 9,452.4 billion, causing a greater social cost loss compared to smoking and obesity (Lee 2020).

Alcohol hangover is one of the toxic consequences of excessive alcohol intake and is commonly experienced across the general population. It comprises a variety of symptoms including drowsiness, concentration problems, dry mouth, dizziness, gastrointestinal complaints, sweating, nausea, hyper-excitability, and anxiety. These symptoms may persist >24 h after blood alcohol levels deplete. The main cause of these hangover symptoms is acetaldehyde, which is an alcohol metabolite (Swift & Davidson 1998). Therefore, it is important to immediately decompose, and thereby, decrease the levels of alcohol and aldehyde present in the body due to drinking, which is a means to reduce the socio-economic losses caused by drinking.

Hovenia dulcis is widely used to relieve hangovers because it helps decompose alcohol, thereby preventing liver damage (Lee et al. 1999). It has been reported that (+)-dihydromyricetin isolated from the fruits of *H. dulcis* is effective in decomposing alcohol and recovering liver function, and 3-methoxy-4-hydrobenzoic acid and 3-methoxy-4-hydroxycinnamic acid isolated from hot water extracts of *H. dulcis* have been reported to exert antioxidant and antibacterial effects (Masayuki et al. 1997; Cho et al. 2000). In addition, theracurmin is a component that improves the low bioavailability of curcumin, and its antioxidant and anti-inflammatory effects have been reported (Ohno et al. 2017; Paik et al. 2019).

Although there have been reports of anti-hangover and antioxidant effects of *H. dulcis* and theracurmin, there has been no study on the synergistic effect of the two mixtures

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on the anti-hangover effect. Therefore, we conducted a study to investigate the eliminatory effect of theracurmin drink, a commercial health drink containing extract of *H. dulcis* fruit stalk and theracurmin, on ethanol-induced hangover in rats.

II. Materials and Methods

1. Materials

Theracurmin consisted of 30% curcumin, 6% undisclosed components (curcumin derivatives), 0.7% citric acid, 8.7% dextrin, 14.6% gum ghatti, and 40% maltose. Theracurmin drink is a readyQ® product, manufactured and supplied by Handok. The extract of *H. dulcis* fruit was supplied by SAEROM B&F Co., Ltd. (Cheonan, Korea), and the extract of *H. dulcis* fruit stalk was supplied by SK Bioland Co., Ltd. (Cheongju, Korea). The positive control (PC) used a hangover relieving drink from Company C (Seoul, Korea).

Commercial assay kits for measuring alcohol and acetaldehyde levels were purchased from Roche (Darmstadt, Germany). Commercial assay kits for measuring alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) activity were obtained from BioVision (Mountain View, CA, USA). An assay kit for measuring the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was purchased from Asan Pharmaceutical (Seoul, Korea). All other chemicals and reagents, including the total glutathione assay kit, were sourced from Sigma-Aldrich (St. Louis, MO, USA) unless stated otherwise.

2. Animals

Male Sprague Dawley rats (150-180 g; 6-weeks-old) were supplied by Orient Bio Inc. (Gyeonggi-do, Korea). All mice were housed in polycarbonate cages at 23±3°C and 55±15% humidity and fed standard laboratory chow and water *ad libitum*. Six rats per group were used throughout the experiments after an initial acclimation period of at least 1 week. All animal experiments were approved by The Committee for the Care and Use of Laboratory Animals in Eulji University, and performed in accordance with the Eulji University Guidelines for Laboratory Animals Care and Usage (EUIACUC19-23).

3. Preparation of experimental ethanol-induced hangover rats

For the hangover rat model, 40% ethanol (5 g/kg body weight) was administered orally once, as described previously (Kato et al. 1990). Samples to confirm the anti-hangover effect were orally administered 30 min before ethanol administration. Then one of the following was administered to the test rats: theracurmin drink, 10 mL/kg; the extract of *H. dulcis* fruit, 100 mg/kg; the extract of *H. dulcis* fruit stalk, 100 mg/kg; theracurmin, 69 mg/kg; a positive control, 300 mg/kg <Table 1>. To measure alcohol and acetaldehyde concentrations in the blood of rats at 1, 3, and 5 h post-ethanol injection, 100 μL blood samples were drawn from each rat via orbital puncture and centrifuged at 6,000 rpm for 20 min at 4°C. At 24 h post-ethanol injection, the rats were

<Table 1> Composition of test group

	Sex	Number of mice	Dose	FE content	FSE contnet	TC content	Yeast extract content
N[1)]	male	6	-	-	-	-	-
NC[2)]	male	6	-	-	-	-	-
TD[3)]	male	6	10 mL/kg	-	10 mg/mL	1.66 mg/mL	-
TC[4)]	male	6	69 mg/kg	-	-	1 mg/mg	-
FE[5)]	male	6	100 mg/kg	1 mg/mg	-	-	-
FSE[6)]	male	6	100 mg/kg	-	1 mg/mg	-	-
PC[7)]	male	6	10 mL/kg	7.15 mg/mL	-	-	N.I.*

[1)]N: Normal
[2)]NC: saline alone
[3)]TD: theracurmin drink
[4)]TC: theracurmin
[5)]FE: fruit extract of Hovenia dulcis
[6)]FSE: fruit stalk extract of Hovenia dulcis
[7)]PC: positive control
*N.I., Not Indicated

euthanized, and the liver tissues were dissected, cleaned, and washed in ice-cold phosphate buffered saline for analysis.

4. Measurement of blood alcohol and acetaldehyde levels in hangover-induced rats

Serum alcohol and acetaldehyde levels collected over time were analyzed according to previously reported methods (Bucher & Redetzki 1951; Lundquist, 1974) using an assay kit for measuring ethanol and acetaldehyde (Roche Co., Darmstadt, Germany). A spectrophotometer (BioTek, Winooski, VT, USA) was used for analysis. The alcohol and acetaldehyde content of each group was calculated using the formula presented in the kit, and the data for each group were presented as relative activity (%) based on the serum alcohol and acetaldehyde content after 1 h in the control group.

5. Measurement of ADH and ALDH activity in liver tissue

0.1 M Tris-HCl buffer (pH 7.4) corresponding to 10 times the liver weight (g) was added and homogenized on ice with a glass Teflon grinder. ADH and ALDH activities in the liver tissue homogenate were measured by NAD^+ reduction via colorimetry using an assay kit (BioVision), and expressed in mU/mL, according to the calculation formula presented in the kit.

6. Measurement of enzyme activity indicating liver function in serum and liver

The activities of AST and ALT were measured using an assay kit (Asan Pharmaceutical) prepared by a colorimetric method using an enzyme reaction with each substrate in serum and liver tissue homogenate. Enzyme activity was expressed in Karmen units.

7. Measurement of total glutathione

Levels of total hepatic glutathione were quantified using a total glutathione assay kit from Sigma Chemical Co., according to the manufacturer's recommended protocol.

8. Clinical study

This clinical trial was conducted as a randomized, double-blind, placebo-controlled. Among all subjects (a healthy adult male over 19 years old, a man who feels hangover symptoms when taking a bottle of *soju*), those with gastrointestinal disorders (e.g., Crohn's disease, pancreatitis, gout), those with anemia, liver disease, those who continuously ate foods containing curcumin, and those who continuously consumed functional foods containing curcumin excluded.

112 subjects who met the criteria were randomly selected on the day of the human application test. The subjects ate a breakfast of about 600 kcal, equivalent to 1 calorie per meal, 2 hours and 30 minutes before the start of drinking, and consumed the pre-allocated human test product (100 mL each was taken per intake) 30 minutes before drinking. Drinking was a minimum snack (20 shrimp crackers), soju 450 mL (alcohol 72 g, ethanol content 20.1%) was consumed within 30 minutes, and fasting was maintained for 8 hours after drinking. To check blood alcohol concentration, blood was collected 1 hour before and after 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 6 and 8 hours after drinking. This study was approved by the Institutional Review Boards at Bundang Jesaeng General Hospital (IMG14-06).

9. Statistics

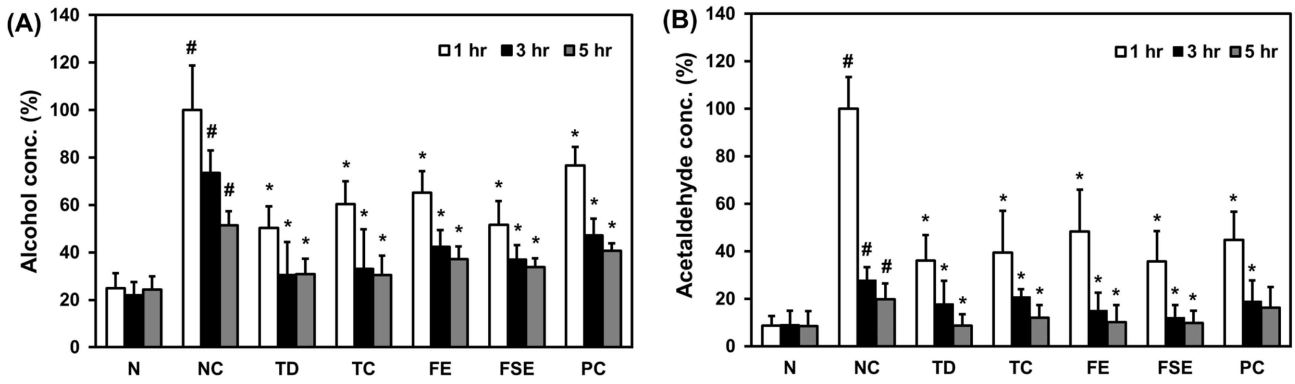
All results are shown as mean±standard deviation. Statistical significance was analyzed using one-way analysis of variance (ANOVA) followed by *post-hoc* analysis using Dunnett's comparison test. Differences at $p<0.05$ were considered to be statistically significant.

III. Results and Discussion

1. Inhibition of blood alcohol and acetaldehyde effects in hangover-induced rats by theracurmin drink

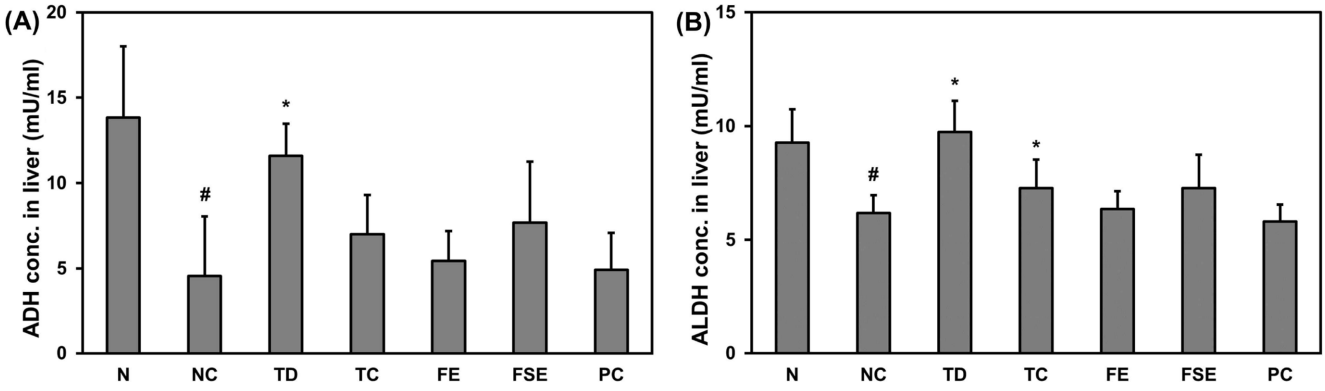
Upon evaluating blood alcohol levels after 1, 3, and 5 h of ethanol administration, we observed that theracurmin drink significantly reduced serum alcohol concentrations compared to the negative control. Blood alcohol levels were reduced by 49.6, 58.6, and 39.7% at 1, 3, and 5 h post-ethanol administration, respectively, compared to the negative controls at each time point. Blood acetaldehyde levels decreased by 63.9, 35.9, and 56.3%, at 1, 3, and 5 h post-ethanol administration, respectively, compared to the negative controls at each time point. The extract of *H. dulcis* fruit and fruit stalk also reduced blood alcohol concentrations, and the effect was greater for the fruit stalk extract. The extract of fruit stalk reduced alcohol concentrations by 48.4, 58.6, and 34.1%, respectively, at 1, 3, and 5 h post-ethanol administration, respectively, compared to the negative controls at each time point, while the fruit extract decreased by 34.9, 42.5, and 27.5%, respectively. Acetaldehyde concentrations also showed the same trend <Figure 1>.

H. dulcis exhibits alcohol decomposition and liver damage preventative effects, so it is included in various health drinks to relieve hangover (Lee et al. 1999), whereas differences in



<Figure 1> Alcohol and acetaldehyde levels in the blood of hangover-induced rats.

Except in the vehicle only treated normal group (N), 40% ethanol was administered in the NC, TD, TC, FE, FSE, PC groups. Each sample (NC, saline alone; TD, theracurmin drink; TC, theracurmin; FE, fruit extract of *Hovenia dulcis*; FSE, fruit stalk extract of *Hovenia dulcis*; PC, positive control) was administered with 40% ethanol 30 minutes after administration, and blood was collected at 1, 3, and 5 hours after ethanol treatment. Alcohol and acetaldehyde concentrations were analyzed in each blood. # <0.05 vs N, * <0.05 vs NC.



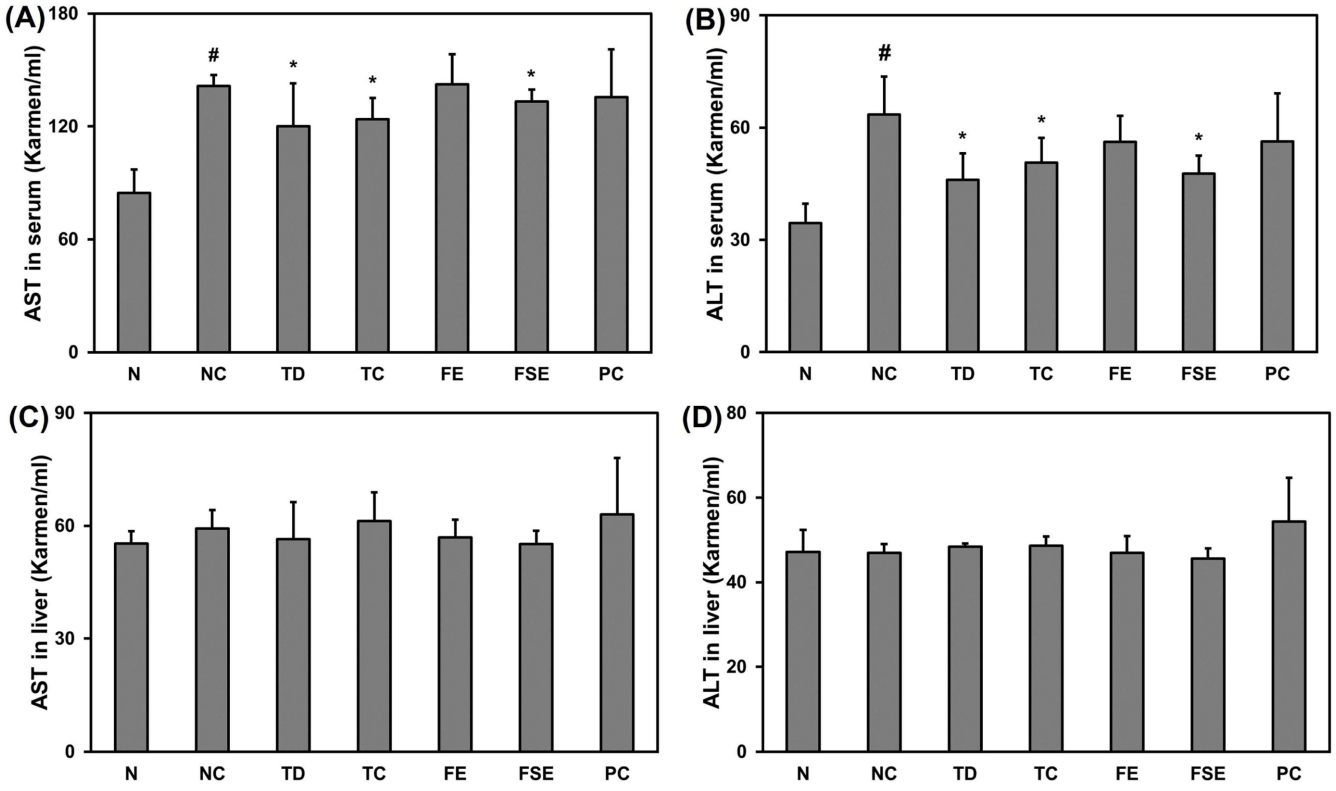
<Figure 2> ADH and ALDH activities in the liver of hangover-induced rats.

Except in the vehicle only treated normal group (N), 40% ethanol was administered in the NC, TD, TC, FE, FSE, PC groups. Each sample (NC, saline alone; TD, theracurmin drink; TC, theracurmin; FE, fruit extract of *Hovenia dulcis*; FSE, fruit stalk extract of *Hovenia dulcis*; PC, positive control) was administered with 40% ethanol 30 minutes after administration. After 24 hours of ethanol administration for induction of hangover, the liver was dissected out. ADH and ALDH were measured in the liver lysate. # <0.05 vs N, * <0.05 vs NC.

the anti-hangover effects involving fruit stalk and fruit have not been compared to date. In this study, to confirm the anti-hangover effect of *H. dulcis* fruit stalk and fruit, we confirmed that administration of fruit stalk extract and fruit altered the concentration of alcohol and acetaldehyde in the blood of rats treated with ethanol. As a result, administration of fruit stalk extract lowered the concentration of alcohol and acetaldehyde in the blood of ethanol-treated rats compared to that of solely the fruit <Figure 1>. Therefore, we think thought that the fruit stalk extract of *H. dulcis* is more suitable as a raw material for the health drink in order to treat the effects of hangover than the fruit extract.

2. Restoring effect of theracurmin drink on alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) levels in liver of hangover-induced rats

Alcohol is metabolized to acetaldehyde by ADH and then to acetate by ALDH (Swift & Davidson 1998). When the activity of these enzymes is high, the decomposition and excretion of alcohol is rapid, so that the hangover can be effectively reduced. Therefore, we confirmed activities of ADH and ALDH in the livers of ethanol-treated rats. Ethanol administered to induce hangover significantly reduced ADH and ALDH activity in the liver of rats. Of the experimental samples administered, only theracurmin drink significantly



<Figure 3> AST and ALT activities in blood and liver of hangover-induced rats.

Except in the vehicle only treated normal group (N), 40% ethanol was administered in the NC, TD, TC, FE, FSE, PC groups. Each sample (NC, saline alone; TD, theracurmin drink; TC, theracurmin; FE, fruit extract of *Hovenia dulcis*; FSE, fruit stalk extract of *Hovenia dulcis*; PC, positive control) was administered with 40% ethanol 30 minutes after administration. To confirm of hepatoprotective effect, the activities of AST and ALT was measured in blood and liver obtained 24 hours after ethanol administration. # <0.05 vs N, * <0.05 vs NC.

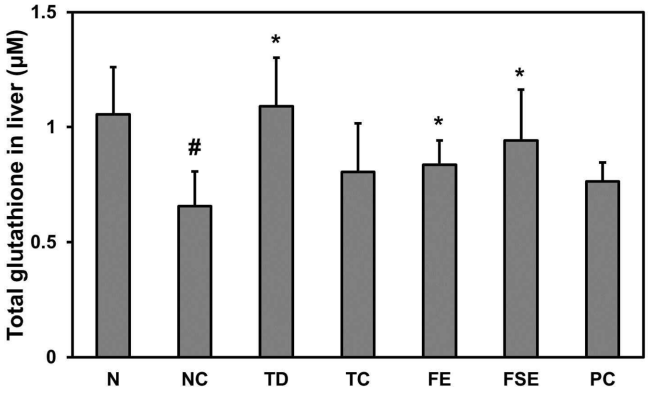
increased both activities <Figure 2>. These results suggested that theracurmin drink can effectively inhibit hangover.

Oral administration of theracurmin drink increased the activities (which had initially been decreased due to alcohol consumption) of ADH and ALDH in rats with ethanol-induced hangover. These effects of theracurmin drink resulted in lower levels of alcohol and acetaldehyde in the blood of these rats <Figure 2>.

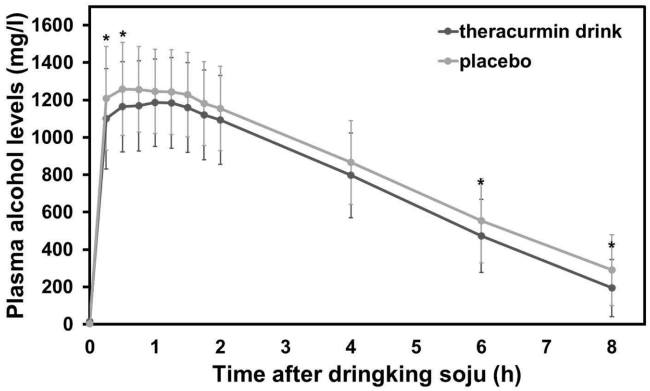
3. Improvement of liver function by theracurmin drink in hangover-induced rats

Alcohol induces liver damage. When the liver is damaged, the activities of AST and ALT in the blood and liver increase. AST and ALT are enzymes that indicate liver function, and increment in their activities indicates decreased liver function (Torruellas et al. 2014). Ethanol administered to induce hangover significantly increased blood AST and ALT levels. Theracurmin drink significantly reduced the activities of AST and ALT, but the extract from the fruit of *H. dulcis* was not effective. The hepatoprotective effect of theracurmin drink, was greater than that of the positive control <Figure 3A, B>. Ethanol administered to rats did not affect liver AST and ALT activity, unlike in blood. Samples containing theracurmin drink had no effect on liver AST and ALT levels <Figure 3C, D>. Indeed, severe liver damage increases ALT in both serum and liver tissue (Thulin et al. 2016). However, single dose of 40% ethanol (5 g/kg body weight) increased AST and ALT in serum, but did not affect AST and ALT in liver tissue. This result may suggest that temporary liver damage does not affect AST and ALT in liver tissue. It is necessary to evaluate the AST and ALT in liver tissue through a long-term experiment.

In conclusion, these results indicated that theracurmin drink has hepatoprotective effects. Additionally, it is believed that the administration of theracurmin drink does not significantly affect normal liver function, as there was no significant difference in AST and ALT activity in liver compared to normal mice. Low doses of curcumin protect alcohol-induced liver damage by modulation of the alcohol metabolic pathway, CYP2E1 and AMPK (Lee et al. 2013a).



<Figure 4> Total glutathione in the liver of hangover-induced rats.
Except in the vehicle only treated normal group (N), 40% ethanol was administered in the NC, TD, TC, FE, FSE, PC groups. Each sample (NC, saline alone; TD, theracurmin drink; TC, theracurmin; FE, fruit extract of *Hovenia dulcis*; FSE, fruit stalk extract of *Hovenia dulcis*; PC, positive control) was administered with 40% ethanol 30 minutes after administration. To confirm the anti-oxidant effect, which can induce anti-hangover effect, of the administered sample, the amount of total glutathione in liver lysate was confirmed. # <0.05 vs N, * <0.05 vs NC.



<Figure 5> Plasma alcohol level after drinking of alcohol in healthy subjects.
The RQ group received theracurmin drink (100 mL each was taken per intake) 30 min before and immediately after drinking alcohol (*soju* 450 mL; alcohol 72 g, ethanol content 20.1%). Values represent mean± SD (n=112). Significantly different at * <0.05.

Also, the extract of fruit stalk of *H. dulcis* with hot water or 70% methanol and followed with 100% methanol, were significantly reduced the CCl_4 or D-galactosamine/LPS induced damage in sliced liver (Na et al. 2004). These liver protective effects of theracurmin drink are estimated to be contributed by the addition of theracurmin, which improves the bioavailability of curcumin and extract from the fruit stalk of *H. dulcis*.

4. Antioxidant effects of theracurmin drink in liver of hangover-induced rats

The oxidative processes involved in alcohol metabolism generate many free radicals that increase oxidative stress. In addition, immunological changes are considered important in the pathogenesis of hangover, as increased inflammatory cytokine production is noted (Jayawardena et al. 2017). Therefore, various antioxidants or anti-inflammatory agents are included in health drinks to remove hangovers. To confirm the mechanism underlying the anti-hangover effects of theracurmin drink, its antioxidant activity was analyzed. Ethanol administered to induce hangover significantly lowered the total glutathione content in liver. This result is consistent with previous reports that alcohol induces hepatic oxidative stress. theracurmin drink restored the total glutathione content to normal levels <Figure 4>. In this study, the anti-hangover effect of theracurmin, which has been reported to have antioxidant and anti-inflammatory effects (Paik et al. 2019; Ohno et al. 2017), was confirmed. Oral administration of theracurmin to ethanol-treated rats significantly reduced the concentration of alcohol and acetaldehyde <Figure 1>. This result reinforces recent reports that antioxidants have an anti-hangover effect (Jayawardena et al. 2017). In conclusion, theracurmin drink exerts an antioxidant effect and suggested that this effect induces an anti-hangover effect.

5. Plasma alcohol levels in clinical trials

Blood alcohol levels are shown in <Figure 5>. The blood alcohol concentration in the theracurmin drink group was significantly lower than that of the placebo group after 0.25 hr (p=0.0394), 0.5 hr (p=0.0491), 6 hr (p=0.0475) and 8 hr (p=0.0051) drinking alcohol. On the other hand, blood alcohol iAUC from immediately after alcohol consumption to 8 hours after alcohol consumption was also lower in the Ready Q drink group than in the Placebo group, which was statistically significant (p=0.0449) (data not shown). In clinical trials in humans, theracurmin drink showed a significantly lower alcohol concentration than the placebo group after drinking soju <Figure 5>. This result is consistent with animal experiments, and this effect is due to a mechanism proven in animal experiments. The hangover reliever, which has been confirmed to be effective through animal experiments, lowered the blood alcohol level in the same as theracurmin drink in human clinical trials (Lee et al. 2013b). In particular, SM-2015 reported by Shin et al. (2017) significantly suppressed blood alcohol concentration only at 120 minutes after drinking. However, it is considered that

additional studies are needed on the improvement of blood acetaldehyde and hangover symptoms of theracurmin drink in humans.

Recently, several medicines have been developed to reduce and eliminate hangovers that occur after drinking alcohol, but these have their own toxicity and side effects (Coppersmith et al. 2021). Therefore, much attention has been paid to the development of safe health drinks (Park et al. 2006). In this study, the effect of theracurmin drink on hangover was confirmed and the mechanism was revealed. Theracurmin drink exhibits hepatoprotective effects through antioxidant action and increases ADH and ALDH activity, thereby reducing the effects of hangover. These hepatoprotective effects are thought to be due to the combined effects of the *H. dulcis* fruit stalk extract and theracurmin.

In conclusion, theracurmin drink is suggested as a health drink that relieves or prevents hangovers caused by alcohol through increased alcohol metabolism enzyme activity, antioxidant effects and liver protection.

IV. Summary and Conclusion

This study is about the anti-hangover effect of theracurmin drink, a health drink containing the fruit stalk of Hovenia dulcis and theracurmin. Theracurmin drink showed anti-hangover effect by lowering the concentration of ethanol and acetaldehyde in blood samples collected 1, 3, and 5 hours after ethanol administration. These effects are due to the increase of the ADH and ALDH activities involved in the alcohol metabolism of theracurmin drink. In addition, theracurmin drink restored the total glutathione levels decreased by ethanol to normal levels. This result indicates that theracurmin drink exerts a protective effect on the liver through its antioxidant activity. Therefore, theracurmin drink exhibits hepatoprotective effects through antioxidant action and increases ADH and ALDH activity, thereby reducing the effects of hangover. These hepatoprotective effects are thought to be due to the combined effects of the Hovenia dulcis fruit stalk extract and theracurmin. Therefore, theracurmin drink is suggested as a health drink to relieve or prevent alcohol-induced hangover.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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