

Effect of Mixed Fruit and Vegetable Juice on Alcohol Hangovers in Healthy Adults

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ABSTRACT: The purpose of this study was to investigate the effects of mixed fruit and vegetable juice on alcohol hangover in healthy adults in a randomized crossover trial. *Angelica keiskei*/green grape/pear juice (AGP juice) was a mixture of *A. keiskei* juice, green grape juice, and pear juice at 1:1:1 ratio. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) activities of AGP juice were measured *in vitro*. Fifteen healthy adults consumed alcohol (1.25 g/kg weight), and either water (control group) or AGP juice (AGP juice group). Blood was collected and expiratory-air alcohol levels were measured at 0~360 min after drinking the alcohol. Compared with control, AGP juice had higher ADH and ALDH activity *in vitro*. The peak alcohol levels in expiratory-air and plasma after drinking AGP juice were significantly lower than those after drinking water. The area under the curves for expiratory-air and plasma alcohol of the AGP juice group were lower than those of the control group. Thirst and headache scores after intake of alcohol were significantly reduced by AGP juice consumption compared with the control group. These data demonstrated that AGP juice could contribute to eliminate alcohol toxicity and hangover symptoms by enhancing alcohol metabolizing enzyme activities.

Keywords: alcohol, hangover, alcohol metabolizing enzyme, healthy subjects, juice

INTRODUCTION

Alcohol is the main risk factor in liver disease, including fatty liver, alcoholic hepatitis, and cirrhosis (1). Excessive alcohol consumption is also associated with increased incidence of cancer and cardiovascular disease (2). It was reported that the alcohol-induced mortality rate for the total population was 9.3%. In particular, alcohol-related liver disease deaths increased from 3,600 per 100,000 in 2005 to 3,872 per 100,000 in 2015 (3).

The average annual alcohol consumption per capita in Korea is 9.3 L, which is relatively high compared with the 9.0 L per capita in Organization for Economic Cooperation and Development (OECD) countries (4). In the 2014 Korea National Health and Nutrition Examination Survey, 60.5% of adults consumed alcohol monthly (75.3% of men, 45.7% of women), and the rates of high-risk drinking were 19.7% in men and 5.4% in women (5).

More than 90% of alcohol is primarily metabolized in the liver, and the rest is eliminated via the kidneys and lungs (6). The three alcohol metabolic pathways in the body involve alcohol dehydrogenase (ADH), the microsomal ethanol oxidation system (MEOS), and catalase

(7-9). Most alcohol is first metabolized by ADH into acetaldehyde, which is converted into acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde, a major toxic metabolite, increases hepatic lipid peroxidation and oxidative stress, thereby aggravating liver damage (7,8). Under excessive and chronic alcohol intake, 10~20% of the absorbed alcohol is metabolized by the MEOS, which utilizes the cytochrome P450 2E1 (CYP2E1) enzyme. The CYP2E1 pathway increases reactive oxygen species, including hydrogen peroxide, hydroxyl radical, and superoxide, which can lead to liver damage by reacting with lipids, proteins, and DNA (7-9). Thus, improvement of antioxidant capacity is important to prevent liver injury against oxidative stress.

Alcohol hangover symptoms are characterized by diverse physical and psychological symptoms including drowsiness, difficulty concentrating, dry mouth, dizziness, gastrointestinal complaints, sweating, nausea, hyperexcitability, and anxiety (6,10,11). Intake of excessive alcohol can lead to hangover symptoms due to acetaldehyde that is generated by ADH (6,10). Therefore, the elimination of acetaldehyde by promoting the activity of alcohol-metabolizing enzymes can help relieve hangover

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symptoms.

Natural products containing fruit, vegetable, and herbal substances increased alcohol degrading enzyme activities and have been reported to alleviate alcohol hangover symptoms. Dandelion (12), pear (13), tomato (14), red ginseng (15), *Hovenia dulcis* (16), and *Opuntia ficus indica* (17) are reported to relieve hangovers by stimulating alcohol metabolism and have antioxidant effects on alcohol-induced oxidative stress.

In a previous study, we measured the effect of various fruit and vegetable juices on alcohol-degrading enzymes *in vitro* (18). Among them, *Angelica keiskei* juice and green grape juice strongly enhanced the activities of ADH and ALDH *in vitro* (18). However, the effects of *A. keiskei* juice and green grape juice on preventing hangover symptoms have not been reported. *A. keiskei* juice mixed with green grape juice is not palatable because of its bitterness and flavor. Korean pear (*Pyrus pyrifolia* cv. *Shingo*) is reported to promote the activities of ADH and ALDH *in vitro* (13) and has a sweet taste due to the high content of sugar. Therefore, we mixed *A. keiskei*/green grape juice with pear juice to improve its taste and flavor. *A. keiskei*/green grape/pear (AGP) juices were prepared by mixing *A. keiskei* juice, green grape juice, and pear juice in a ratio of 1:0.5:1, 1:1:0.5, and 1:1:1 and conducted sensory evaluation. AGP juice mixed at 1:1:1 ratio exhibited the highest scores of sensory acceptability for texture, flavor, and overall preference.

In this study, we examined the effects of AGP juice on reducing hangovers in healthy subjects.

MATERIALS AND METHODS

Preparation of mixed fruit and vegetable juice

A. keiskei, green grape, and pear were purchased from a market in Gimhae, Korea and washed with tap water. Juices of *A. keiskei*, green grape, and pear were prepared using a low-speed masticating juicer (HH-SBF11, Hurom Co., Ltd., Gimhae, Korea). AGP juice was a mixture of *A. keiskei* juice, green grape juice, and pear juice at 1:1:1 ratio.

Determination of alcohol degrading enzyme activities *in vitro*

Alcohol dehydrogenase activity was measured using the method described by Blandino et al. (19). Briefly, the reaction mixture consisted of 1.4 mL distilled water, 750 μ L 1.0 M Tris-HCl buffer (pH 8.8), 300 μ L 20 mM nicotinamide adenine dinucleotide (NAD⁺), 300 μ L ethanol, and 100 μ L juice. Then, 150 μ L ADH was added to the reaction mixture and incubated at 30°C for 5 min. After incubation, the absorbance was measured at 340 nm for 10 min at 30 s intervals using a microplate reader (model

550, Bio-Rad Laboratories Inc., Hercules, CA, USA). Aldehyde dehydrogenase activity was determined according to the method of Bostian and Betts (20). Briefly, the reaction mixture consisted of 2.1 mL distilled water, 300 μ L 1.0 M Tris-HCl (pH 8.0), 100 μ L 20 mM NAD⁺, 0.1 M acetaldehyde, 100 μ L 3.0 M KCl, 100 μ L 0.33 M 2-mercaptoethanol, and 100 μ L juice. First, 100 μ L ALDH was added to the reaction mixture, which was incubated at 30°C for 5 min. After incubation, the absorbance was measured at 340 nm for 10 min using a microplate reader. The increase in absorbance from time zero was measured, and the activities of ADH and ALDH were calculated as a percentage of the blank control. The measurements were performed in triplicate.

Determination of total polyphenol content and DPPH radical scavenging activity

The total polyphenol content was measured following the method of Folin and Denis (21). First, 1 mL AGP juice was added to 4 mL of methanol, incubated for 5 h at 4°C in the dark, and centrifuged at 850 g for 20 min. The supernatant (400 μ L) was mixed with Folin-Ciocalteu reagent (200 μ L), and then incubated for 3 min at room temperature. Then, 400 μ L of 2% Na₂CO₃ was added to the mixture, and allowed to incubate for 60 min. The absorbance was recorded at a wavelength of 750 nm using a spectrophotometer (Libra 22, Biochrom, Cambridge, UK), and the total polyphenol content was quantified using tannic acid as a standard. The results were expressed as mg of tannic acid equivalents (TAE) per 100 mL of AGP juice. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity was measured using the method described by Blois (22). Briefly, 800 μ L of DPPH solution (0.1 mM) prepared in 80% ethanol was added to an aliquot (200 μ L) of AGP juice after centrifugation at 850 g for 10 min. The absorbance was measured at 517 nm at room temperature after 10 min. Analyses were performed in triplicate.

Clinical trials

Fifteen healthy adults (11 men and 4 women; 29.3 \pm 7.0 years old) participated in a randomized double-blind crossover trial. Informed consent was obtained from all subjects before participation. The exclusion criteria were pregnancy, breast-feeding, intestinal disorders, liver disease, diabetes mellitus, cardiovascular disease, cancer, or any other serious disorder requiring regular medical treatment. The study was conducted in a randomized crossover design. The subjects were asked to abstain from drinking for 3 days and to fast for 12 h before each study. During testing, the 15 subjects were divided into control and AGP juice groups. At the first visit, the subjects drank 240 mL of water or AGP juice 30 min before drinking alcohol. The subjects consumed alcohol (1.25

g/kg weight) and 100 g of silken soy curd and drank water or AGP juice immediately afterwards. Blood samples were taken 0, 30, 60, 120, and 360 min after drinking the alcohol and water or AGP juice. Expiratory-air alcohol levels were measured 0, 30, 60, 120, 240, and 360 min after alcohol consumption using a breathalyzer (Sentech Korea Corp., Paju, Korea). At the second visit, the subjects followed the same protocol, and the control and AGP juice treatments were switched between the two groups. The Institutional Review Board of Inje University (No. 2-1041024-AB-N-01) approved the study protocol.

Anthropometric and biochemical measurements were performed in all subjects before the start of the study. Body weight and height of the subjects were measured in the morning. Body mass index was calculated as body weight in kilograms divided by height in meters squared. Body fat content was measured with a bioimpedance analyzer (HBF-300, Omron Corporation, Kyoto, Japan). Blood was centrifuged at 3,000 g for 10 min. Plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured enzymatically using commercial kits (Asan Pharmaceutical, Seoul, Korea). Plasma alcohol and acetaldehyde levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Abcam, Cambridge, UK).

Hangover symptoms were determined by a survey from hangover assessment tools (23,24) at 360 min after alcohol consumption in each trial. The questionnaires consisted of 6 questions addressing thirst, sleepiness, headache, dizziness, nausea, and stomach pain. The scores ranged from 0 (symptoms absent) to 5 (extremely severe symptoms) and covered the 6 stages.

Statistical analysis

All data are expressed as the mean±standard error of the mean (SE). Differences among the groups were analyzed by a one-way analysis of variance (ANOVA) followed by Tukey's test ($P<0.05$) using the SAS program (ver. 9.2, SAS Institute Inc., Cary, NC, USA). Student's *t*-test was used to evaluate the significance ($P<0.05$) of differences between the mean values of the control and AGP groups.

RESULTS

Alcohol degrading enzyme activities *in vitro*

The influence of AGP juice on ADH and ALDH activities *in vitro* is shown in Fig. 1. ADH activities of *A. keiskei* juice, green grape juice, and pear juice were 119.2 ± 2.8 , 124.6 ± 2.2 , and $112.9\pm 3.3\%$, respectively. ALDH activities of *A. keiskei* juice, green grape juice, and pear juice were 110.1 ± 2.5 , 115.2 ± 2.8 , and $106.7\pm 2.3\%$, respectively. AGP juice increased ADH and ALDH activities by

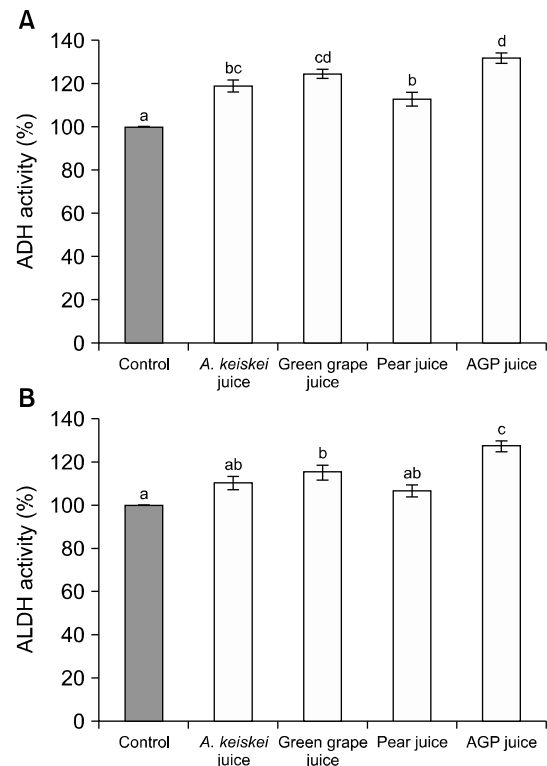


Fig. 1. Activities of alcohol dehydrogenase (A) and aldehyde dehydrogenase (B) of AGP juice *in vitro*. Values represent mean±SE (n=3). Each bar with different letters (a-d) is significantly different at $P<0.05$.

$132.0\pm 2.4\%$ and $127.4\pm 2.1\%$, respectively. In this study, alcohol degrading enzyme activities of AGP juice may have a synergic effect rather than a single juice alone.

Antioxidant effects

The total polyphenol content and DPPH radical scavenging activity of AGP juice are shown in Table 1. The total polyphenol content of the AGP juice was 20.3 ± 0.1 mg TAE/100 mL juice. The DPPH radical scavenging activity of AGP juice was $83.4\pm 0.2\%$.

General characteristics

In this study, we evaluated the effects of AGP juice on alcohol metabolism and hangover symptoms in healthy subjects. Characteristics of the subjects are given in Table 2. The average age of the subjects in this study were 29.3 ± 7.0 years. The ALT and AST activities of the subjects, biochemical markers of liver damage, were in the

Table 1. Total polyphenol content and DPPH radical scavenging activity of *Angelica keiskei*/green grape/pear (AGP) juice

	Total polyphenol content (mg TAE/100 mL juice)	DPPH scavenging activity (%)
AGP juice	20.3 ± 0.1	83.4 ± 0.2

Values represent mean±SE of triplicate experiments. DPPH, 1,1-diphenyl-2-picrylhydrazyl; TAE, tannic acid equivalents.

Table 2. General and biochemical characteristics of healthy subjects

Parameters	
Height (cm)	173.4±1.6
Weight (kg)	75.5±3.2
Body mass index (kg/m ²) ¹⁾	25.1±0.9
Body fat (%)	25.9±1.4
Alanine aminotransferase (U/L)	13.9±2.4
Aspartate aminotransferase (U/L)	18.9±1.4
Alcohol consumption (g/d)	28.0±5.6

Values represent mean±SE (n=15).

¹⁾Body mass index (kg/m²)=body weight (kg)/height (m)².

normal range. The average consumption of alcohol of subjects was 28.0±5.6 g/d.

Expiratory-air alcohol and plasma alcohol and acetaldehyde levels

The increase of expiratory-air alcohol and plasma alcohol and acetaldehyde levels are shown in Fig. 2. The area under the alcohol and acetaldehyde response curves are shown in Table 3. The incremental expiratory-air alcohol levels of the control and AGP juice groups reached a

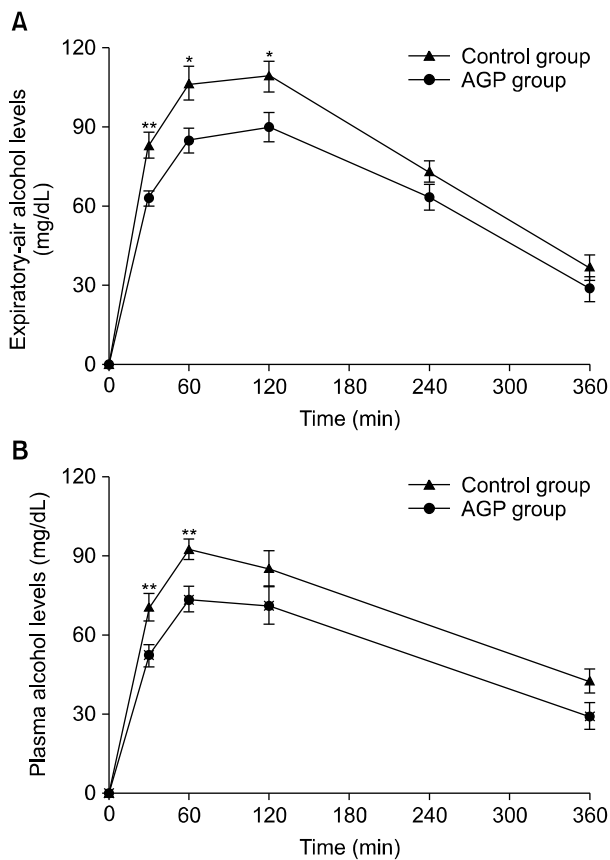


Fig. 2. Increase of expiratory-air alcohol (A) and plasma alcohol (B) after drinking of alcohol in healthy subjects. The control and AGP juice groups received 240 mL of water (control group) or AGP juice (AGP juice group) 30 min before and immediately after drinking alcohol (1.25 g/kg weight). Values represent mean±SE (n=15). Significantly different at * $P<0.05$, ** $P<0.01$.

Table 3. Area under the curves for alcohol and acetaldehyde response in healthy subjects

Group ¹⁾	Control	AGP juice
Expiratory-air alcohol (mg·h/dL)	468.3±22.6*	385.9±26.2
Plasma alcohol (mg·h/dL)	401.9±23.4*	317.3±28.3
Plasma acetaldehyde (mg·h/dL)	1.26±0.03	1.14±0.05

Values represent mean±SE (n=15).

*Significantly different at $P<0.05$.

¹⁾The control and *Angelica keiskei*/green grape/pear (AGP) juice groups received 240 mL of water (control group) or AGP juice (AGP juice group) 30 min before and immediately after drinking alcohol (1.25 g/kg weight).

maximum of 109.3±5.9 and 90.0±5.6 mg/dL at 120 min, respectively. The consumption of AGP juice significantly reduced the expiratory-air alcohol levels at 30 ($P<0.01$), 60, and 120 ($P<0.05$) min compared with the control group. The area under the curve (AUC) for the expiratory-air alcohol response of the AGP juice group (385.9±26.2 mg·h/dL) was lower than that of the control group (468.3±22.6 mg·h/dL, $P<0.05$). The incremental plasma alcohol levels of the control and AGP juice group reached a peak of 92.5±4.0 and 73.5±5.0 mg/dL at 60 min, respectively. AGP juice significantly alleviated the increase in plasma alcohol levels at 30 and 60 min compared with the control group ($P<0.01$). The AUC for the plasma alcohol response was significantly ($P<0.05$) lower in the AGP juice group (317.3±28.3 mg·h/dL) than in the control group (401.9±23.4 mg·h/dL). The plasma acetaldehyde levels of the control and AGP juice groups reached a maximum of 0.31±0.01 and 0.28±0.01 mg/dL at 120 min, respectively (Fig. 3). The incremental plasma acetaldehyde levels and the AUC for the acetaldehyde response of the two groups were not significantly different.

Alcohol hangover symptoms

Scores of hangover conditions of the subjects are given

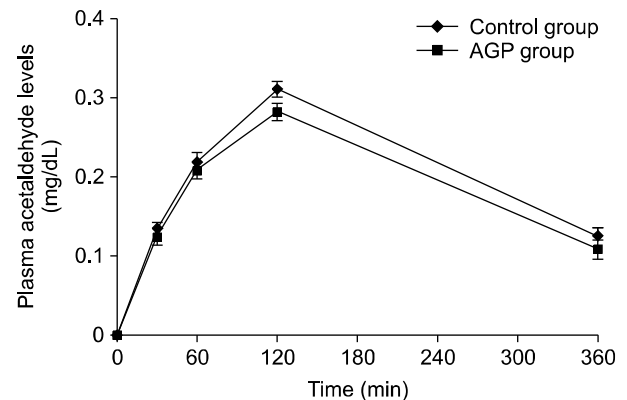


Fig. 3. Increase of plasma acetaldehyde after drinking of alcohol in healthy subjects. The control and AGP juice groups received 240 mL of water (control group) or AGP juice (AGP juice group) 30 min before and immediately after drinking alcohol (1.25 g/kg weight). Values represent mean±SE (n=15).

Table 4. Scores of hangover conditions in healthy subjects

Group ¹⁾	Control	AGP juice
Thirst	3.1±0.3*	2.1±0.2
Sleepiness	2.7±0.3	2.6±0.2
Headache	2.9±0.2*	2.0±0.2
Dizziness	3.0±0.3	2.3±0.4
Nausea	1.6±0.3	1.5±0.2
Stomach pain	1.2±0.2	1.2±0.1

Values represent mean±SE (n=15).

*Significantly different at $P<0.05$.

¹⁾The control and *Angelica keiskei*/green grape/pear (AGP) juice groups received 240 mL of water (control group) or AGP juice (AGP juice group) 30 min before and immediately after drinking alcohol (1.25 g/kg weight). The scores ranged from 0 (symptom absent) to 5 (extremely severe symptom).

in Table 4. Consumption of AGP juice significantly decreased thirst (2.1±0.2) and headache (2.0±0.2) scores compared with the control group (3.1±0.3 and 2.9±0.2, respectively, $P<0.05$). Sleepiness, dizziness, nausea, and stomach pain of the AGP group were not significantly different from the control group.

DISCUSSION

Alcohol is converted into acetaldehyde by ADH, and acetaldehyde is metabolized into acetate by ALDH (8). Alcohol metabolites, especially acetaldehyde, contribute to alcohol hangover symptoms and alcoholic liver disease (1, 7,10). Accelerating the clearance of alcohol and acetaldehyde can decrease 'alcohol toxicity' (7,8).

The consumption of AGP juice effectively attenuated the increase of alcohol levels in plasma and expiratory-air after ingestion of alcohol and decreased the AUC in healthy subjects. Plasma acetaldehyde levels of the AGP juice group tended to be lower than the control group, although the differences were not significant. Acetaldehyde is responsible for hangover symptoms (10). A hangover involves various physical and psychological symptoms following excess alcohol intake. AGP juice improved headache and thirst symptoms after consumption of alcohol. Alcohol hangover symptoms were relieved by increasing the activities of alcohol degrading enzymes (13). It was reported that elevation of the activities of alcohol metabolizing enzymes could be beneficial in eliminating of alcohol metabolites (13,15,25). Several natural products have been reported to reduce the levels of blood alcohol metabolites by increasing the activities of alcohol degrading enzymes, including Korean pear juice (13), red ginseng (15), and herbal mixture (25). Lee et al. (13) demonstrated that Korean pear juice may improve alcohol detoxification by stimulating the activities of ADH and ALDH. In another study, a herbal mixture extract of *Viscum album* L., *Lycium chinense* L., *Inonotus obliquus*, and

Acanthopanax senticosus H. alleviated alcohol hangover symptoms by reducing plasma alcohol levels in healthy adult males (25). In the present study, AGP juice increased ADH and ALDH activities by 32.0% and 27.4% *in vitro*, indicating that alcohol and acetaldehyde are degraded rapidly after alcohol consumption, which prevents accumulation of alcohol metabolites. Thus, AGP juice may enhance alcohol metabolism by increasing ADH and ALDH activities. These data demonstrated that reduced plasma alcohol levels by consumption of AGP juice could contribute to eliminate alcohol toxicity.

AGP juice exhibited strong DPPH radical scavenging activity possibly because of its high polyphenol content. Polyphenols scavenge free radicals directly and thus exert strong antioxidant effects (26). This result is similar to previous research, which showed that the phenolic content had a positive correlation with the antioxidant capacity to scavenge the DPPH radical. Apple juice, grape juice, pineapple juice, and orange juice have high levels of total phenolic compounds and radical scavenging activities (27,28). Parsley juice has been known to be rich in phenolic contents and to exhibit strong antioxidant activity (29).

Alcohol abuse promotes reactive oxygen superoxide accumulation by depleting mitochondrial glutathione levels and, subsequently, increase oxidative stress (30,31). Increased oxidative stress can lead to suppressing ALDH activity, resulting in decreasing acetaldehyde clearance (20,32). Improvement of antioxidant status may be beneficial to prevent the reduction of ALDH activity and facilitate the metabolism of acetaldehyde, via reducing alcohol-induced oxidative stress. *A. keiskei* has long been used as a herbal medicine due to its antioxidant effects (33). *A. keiskei* contains bioactive substances, such as chalcone, coumarin, saponin, and flavonoids (34,35). Several studies have demonstrated that *A. keiskei* extract has beneficial effects on alcoholic liver diseases (34), antioxidant (33), anti-cancer (35), and anti-inflammatory effects (36). *A. keiskei* extract was reported to prevent D-galactosamine-induced hepatic failure in rats (37). Chronic consumption of *A. keiskei* extract improved liver function in habitual alcohol drinkers (34). It was suggested that antioxidant substances of *A. keiskei* could contribute to the hepatoprotective effects. Phenolic compounds in grape (38,39) and pear (40) have been reported to decrease oxidative stress by scavenging free radicals and inhibition of lipid peroxidation. Therefore, AGP juice may contribute to improve antioxidant status via reducing oxidative stress.

The limitation of this study may be a placebo effect by consumption of water instead of placebo juice in the control group. Since plasma ADH and ALDH activities were not measured, we could not elucidate the mechanisms for the beneficial effects in improving alcohol hangover

in healthy subjects. Further study is necessary to understand the underlying mechanisms of action by measuring the activity or gene expression of alcohol metabolism enzymes.

In conclusion, AGP juice reduced plasma levels of alcohol metabolites and hangover symptoms in healthy adults by enhancing alcohol-metabolizing enzyme activities and exerting antioxidant effects. Thus, AGP juice may be helpful in alleviating alcohol hangover symptoms.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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