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Clinical effect of a polysaccharide-rich extract of *Acanthopanax senticosus* on alcohol hangover

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The present study aimed to examine the effects polysaccharide-rich extract of *Acanthopanax senticosus* (PEA) on blood alcohol concentration (BAC) and hangover as well as blood lab parameters. A randomized, placebo-controlled, double-blind crossover trial was conducted. The PEA was orally administered before and after consuming alcohol 1.75 g/kg of pure alcohol. After alcohol consumption, BAC was measured for evaluation of alcohol pharmacokinetics. In the second day morning, subjects were asked to complete the Acute Hangover Scale (AHS) questionnarie. BAC results showed little difference between placebo and PEA groups, indicating that PEA does not have an effect on the pharmacokinetics of alcohol. However, several AHS items (i.e., tired, headache, dizziness, stomachache and nausea) and AHS total score were significantly improved by PEA. Blood lab parameters were significantly altered by alcohol in the placebo group. The alteration by alcohol of glucose and C-reactive protein (CRP) level was significantly attenuated by PEA. Therefore, PEA may have potential to reduce the severity of the alcohol hangover by inhibiting the alcohol-induced hypoglycemia and inflammatory response.

1. Introduction

Hangover is a frequent experience among alcohol consumers (Harburg et al. 1993; Meilman et al. 1990). Hangover develops when blood alcohol concentration (BAC) returns to zero and is defined as the presence of physical and mental symptoms, including headache, dizziness, thirst, anorexia, fatigue, nausea, and hyperexcitability (Verster 2008; Wiese et al. 2000). Hangover-related absenteeism and reduced productivity result in substantial economic loss (Crofton 1987; Single et al. 1998; Stockwell 1998). Despite the high prevalence and economic burden, biological mechanism and effective treatments of alcohol hangover are not well established (Penning et al. 2010).

The search for alcohol hangover cures lasts as long as alcohol is consumed. Although folk remedies and prophylactic agents are available, scientific evidence for their effectiveness is generally lacking (Pittler et al. 2005; Verster and Penning 2010). Several agents and plant extracts to treat hangover have undergone scientific evaluation (Bogin et al. 1987; Chauhan and Kulkarni 1991; Kaivola et al. 1983; Khan et al. 1973; Myrsten et al. 1980; Seppala et al. 1976; Wiese et al. 2004; Ylikahri et al. 1976). Prophylactic use of vitamin B6 and tolfenamic acid, a prostaglandin inhibitor, reduced hangover symptoms (Kaivola et al. 1983; Khan et al. 1973). Extract of the *Opuntia ficus-indica* also showed some effects on individual symptoms (Wiese et al. 2004). In an experimentally induced hangover rat model, glutathione-enriched yeast and rice embryo/soybean extracts showed preventive effects on hangover via antioxidant activity (HS Lee et al. 2009). These works suggest that oxidative stress and inflammatory responses would contribute to hangover symptoms.

Acanthopanax senticosus (AS) belongs to the Ginseng family, Araliaceae, and is widely distributed throughout Europe and Asia (Phuong et al. 2006). It has been used as a traditional medicine to increase strength and energy, and improve memory. Recent reports have demonstrated that AS possessed anti-oxidant, anti-stress, anti-fatigue and anti-inflammatory activities (Huang et al. 2011; Huang et al. 2010; Lee et al. 2004; Yang et al. 2010). A polysaccharide isolated from AS has been known to be one of the most important components of AS, and has shown to be responsible for bioactivities of AS (Fu et al. 2012; Wang et al. 1992; Zhao et al. 2013). Thus, a polysaccharide-rich extract of *Acanthopanax senticosus* (PEA) may contribute to manage alcohol hangover through its anti-oxidant and anti-inflammatory properties.

In the present clinical, we investigated the effects of PEA on hangover. We evaluated whether PEA modulates BAC, and whether PEA is effective in preventing the symptoms of alcohol hangover. We propose here that PEA may relieve hangover. At least, the protective effect was exerted through inhibiting hypoglycemia and inflammation.

Table 1: Characteristics of the 28 subjects who completed the study protocol

Characteristic	Value
Sex	Male
Age, y	24.6 ± 1.6
Height, cm	173.4 ± 4.8
Weight, kg	70.9 ± 8.6

Values are mean ± SD.

Table 2: Changes in pharmacokinetic parameters of alcohol

	$AUC_{0\text{-}t}$(mg*h/l)	C_{max}(mg%)	T_{max}(h)
Placebo	15.4 ± 5.5	0.13 ± 0.04	53.6 ± 27.5
PEA	15.2 ± 4.6	0.14 ± 0.04	63.2 ± 33.0

Values are mean ± SD. PEA = polysaccharide-rich extract of *Acanthopanax senticosus*

2. Investigations and results

Thirty volunteers were assessed for eligibility. Two volunteers decided not to participate. The remaining 28 volunteers were randomly divided into two groups, placebo and PEA. None of the subjects dropped out of the study. Characteristics of the 28 subjects completing the study are summarized in Table 1.

2.1. Blood alcohol concentration

Before and after alcohol consumption, BAC was measured (Fig. 1). From BAC, we obtained pharmacokinetic parameters such as AUC, C_{max} and T_{max} (Table 2). However, changes in BAC of the PEA group were not statistically different from those of the placebo group. This result demonstrates that PEA does not have an effect on the pharmacokinetics of alcohol.

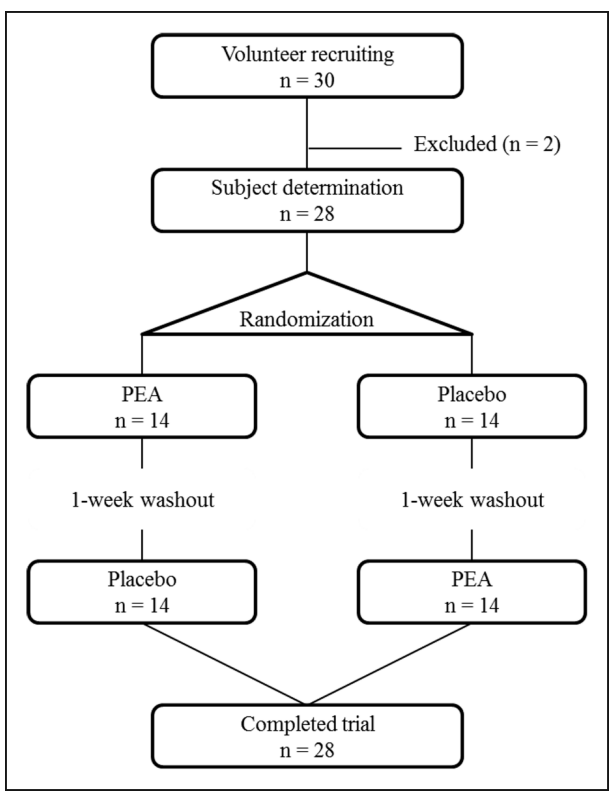

Fig. 1: Profile of trial. PEA = polysaccharide-rich extract of *Acanthopanax senticosus*.

Table 3: Comparison of AHS total and items with placebo and PEA in 28 subjects

Symptom	Placebo	PEA
Hangover	1.8 ± 0.2	1.4 ± 0.1
Thirsty	3.3 ± 0.2	2.9 ± 0.2
Tired	2.5 ± 0.2	1.6 ± 0.1$^{\#\#}$
Headache	2.8 ± 0.2	1.9 ± 0.2$^{\#\#}$
Dizziness, faintness	2.8 ± 0.2	2.0 ± 0.2$^{\#}$
Loss of appetite	1.7 ± 0.2	1.4 ± 0.1
Stomachache	1.9 ± 0.2	1.4 ± 0.1$^{\#}$
Nausea	2.4 ± 0.3	1.5 ± 0.2$^{\#\#}$
Heart racing	1.9 ± 0.2	1.6 ± 0.2
AHS total (mean) score	2.3 ± 0.2	1.7 ± 0.1$^{\#}$

Values are mean ± SD. PEA = polysaccharide-rich extract of *Acanthopanax senticosus*, $^{\#}p < 0.05$ or $^{\#\#}p < 0.01$ *vs*. placebo.

2.2. Hangover symptoms and symptom index score

Among nine AHS items, tired, headache, dizziness, stomachache and nausea were significantly improved by PEA compared with placebo (Table 3). The other symptoms were not significantly affected by PEA, but none was worsened with PEA compared to placebo. Overall, the AHS total mean score was significantly reduced with PEA ($p < 0.05$), suggesting that PEA reduces the severity of hangover symptoms.

2.3. Blood lab parameters

In order to evaluate physiological changes, analysis of blood factors was conducted (Table 4). Among the 14 factors examined, some factors showed significant alteration during the hangover period. In the placebo group, blood levels of glucose, total bilirubin and creatinine were significantly decreased, while levels of BUN, CRP and cortisol were significantly increased. The levels of glucose and CRP were significantly attenuated by PEA.

3. Discussion

In this randomized, placebo-controlled, crossover trial, we found that PEA does not have an effect on the pharmacokinetics of alcohol. However, the decrease in the AHS score by PEA suggested that it has an effect on the pharmacodynamics of alcohol. Comprising reduction in the symptoms of tiredness, headache, dizziness, stomachache and nausea. In the blood parameters, alcohol-induced alterations of CRP and glucose levels were significantly attenuated by PEA.

Alcohol absorption occurs by simple passive diffusion from the gastrointestinal tract. In the organs, mainly the liver, alcohol is metabolized by some enzymes (e.g., alcohol dehydrogense (ADH), aldehyde dehydrogenase (ALDH), cytochrome P450 and catalase). The alcohol elimination process is well known to follow zero-order kinetics. From absorption to elimination of alcohol, the processes are influenced by many factors. Environmental factors (i.e., rate of drinking, food in stomach and type of beverage) can disturb alcohol absorption and alter BAC profile. Alcohol metabolism is altered by genetic factors (i.e., variation in enzymes). Age, gender and smoking also can cause variation in the pharmacokinetics of alcohol (Cederbaum 2012; Hurley and Edenberg 2012).

Table 4: Comparison of physiological measurements under placebo or PEA

	Baseline	Placebo	PEA
Albumin (g/L)	5.03 ± 0.05	4.94 ± 0.06	4.94 ± 0.04
ALP (IU/L)	69.29 ± 5.78	68.96 ± 6.80	73.61 ± 9.76
ALT (IU/L)	18.04 ± 2.09	20.0 ± 2.86	20.79 ± 4.10
AST (IU/L)	17.46 ± 1.00	28.43 ± 10.21	27.89 ± 8.14
BUN (mg/dl)	11.68 ± 0.33	14.43 ± 0.61[@]	14.57 ± 0.58[@]
Cortisol (□g/dL)	13.85 ± 1.05	18.32 ± 1.30[@]	18.10 ± 1.19[@]
Creatinine (mg/dL)	1.07 ± 0.02	0.95 ± 0.02[@]	0.96 ± 0.02[@]
CRP (g/dL))	0.061 ± 0.007	0.078 ± 0.005[@]	0.058 ± 0.01[$]
GGT (IU/L)	18.14 ± 1.60	17.43 ± 1.87	17.11 ± 1.50
Glucose (mg/dL)	95.18 ± 3.06	82.86 ± 1.61[@]	87.68 ± 2.97 [$]
T. bilirubin (mg/dL)	1.06 ± 0.06	0.73 ± 0.06[@]	0.61 ± 0.04[@]
T. cholesterol (mg/dL)	154.96 ± 3.45	162.14 ± 4.03	159.75 ± 3.12
Total protein (g/L)	7.39 ± 0.07	7.39 ± 0.07	7.43 ± 0.06
Uric acid (mg/dL)	5.54 ± 0.21	5.91 ± 0.27	5.96 ± 0.26

Values are mean ± SD. PEA, polysaccharide-rich extract of *Acantopanax senticosus aqueous extract*; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; GGT, gamma glutamyl transferase, [@] $p < 0.01$ vs. baseline, [$] $p < 0.01$ vs. placebo.

This study was designed to evaluate the effect of PEA on symptoms of alcohol hangover experienced by the average alcohol consumer. The study protocol simulated conditions experienced by recreational alcohol consumption. This design is an important component of the study's validity, and improves its generalizability to the average alcohol consumer. The crossover design allowed us to isolate the effect of the intervention, as each subject served as its own control. The rate of consumption, which was regulated by the investigators, was the same in both sessions. Physical activity was not measured during the study sessions but appeared grossly to be the same during the both sessions. Under our conditions, PEA administration did not affect BAC profile suggesting that PEA has no effect on a kinetic of alcohol. Although PEA did not cause a significant change in kinetics, PEA administration showed a significant relief on hangover symptoms. The AHS scores of PEA-treated subjects were distributed at lower score ranges in comparison to those of the placebo group. Furthermore, PEA produced significant changes in blood parameters such as glucose and CRP levels. A significant reduction of glucose levels induced by alcohol coincided with previous reports demonstrating that alcohol may provoke reactive hypoglycemia (Heikkonen et al. 1998; Joffe et al. 1982; Ylikahri et al. 1980). Glucose effectively inhibits the metabolic disturbances induced by ethanol and may affect the symptoms or signs of alcohol intoxication and hangover indirectly (Ylikahri et al. 1976). On the other hand, the elevated CRP levels during the alcohol hangover were decreased by PEA. CRP is a member of the class of acute-phase reactants, as one of inflammation markers (Pepys and Hirschfield 2003). Previous works reported that inflammation may play a role in the pathogenesis of the alcohol hangover, and interrupting inflammatory response could mitigate the symptoms of the alcohol hangover (Kaivola et al. 1983; Kangasaho et al. 1982; JG Wiese et al. 2000). A study conducted in the United States also showed that the CRP levels significantly increased by 50% with hangover in participants who received placebo (Wiese et al. 2004). Based on the results of this study, it is suggested that PEA attenuates hypoglycemia and inflammatory response contributing to the alcohol hangover symptoms.

In spite of all these results, there are several limitations of our study. First, this protocol allowed subjects to consume alcohol consistent with what an average drinker might consume on a heavy night of drinking (5-10 drinks). For safety considerations, the protocol forbids administration of alcohol doses in excess of 1.75 g/kg. Different doses of alcohol groups may be needed for further study to elucidate the precise effects of PEA on hangover. Another limitation is that our protocol served pure alcohol (ethanol concentration of 20%) to subjects. The presence and severity of alcohol hangovers is influenced by many factors other than the amount of alcohol. One of these factors is the presence of congeners in alcoholic drinks. Alcoholic drinks that contain more congeners produce more severe alcohol hangovers (Verster 2008). The effect of PEA may differ in persons consuming different kinds of alcohol. Finally, no women were included in this study, and the effects of PEA in women were not known. Future studies can increase the diversity of the participants.

In conclusion, PEA did not affect BAC profile, but improved the AHS scores and blood lab parameters (glucose and CRP). The symptoms of the alcohol hangover are in part mediated through an inflammatory reaction, demonstrated by elevated CRP levels. Therefore, this study suggests that PEA may have the potential to reduce the severity of the alcohol hangover by inhibiting the alcohol-induced hypoglycemia and inflammatory response.

4. Experimental

4.1. Subjects

Eligible participants were healthy, nonsmoking men, aged 19 to 55 years, with a history of at least once having experienced alcohol-related hangover. Exclusion criteria were a history of hypertension, renal dysfunction, gastrointestinal tract bleeding, peptic ulcer disease, liver disease, cardiac disease, lung disease, active tuberculosis, diabetes, alcohol hypersensitivity, alcoholism, and an allergic reaction to either alcohol or AS. Volunteers were also excluded if they had a history of drug or alcohol abuse. Subjects were instructed not to consume analgesic medications during the 24 hours before the study. Randomization was performed by a person unconnected with the study using a computer-generated random number table. Subject recruiting and randomization profile are summarized in Fig. 2. The study was approved by the institutional review board at College of Medicine, Chung-Ang University, and each participant was given with written informed consent. All participants who applied for enrollment met inclusion and exclusion criteria.

4.2. Preparation of polysaccharide-rich extract of Acanthopanax senticosus (PEA)

Polysaccharide, the main bioactive component, was extracted with optimal techniques using hot water decoction (Nam et al. 2013; Zhang et al. 2007; Zhao et al. 2013). In brief, Fresh AS roots were washed in tap water and air-dried in the shade. Sliced and dried raw materials of AS were blanched at 100 °C for 4 h (43.3 g/l water), and then allowed to cool to room temperature. After cooling, the supernatant was applied to a SephadexG-150 (2.7 × 72 cm) column and bound materials were eluted with a linear gradient of NaCl (0.1 mol/l NaCl). The fractions containing carbohydrate were pooled and precipitated three times with ethanol. The

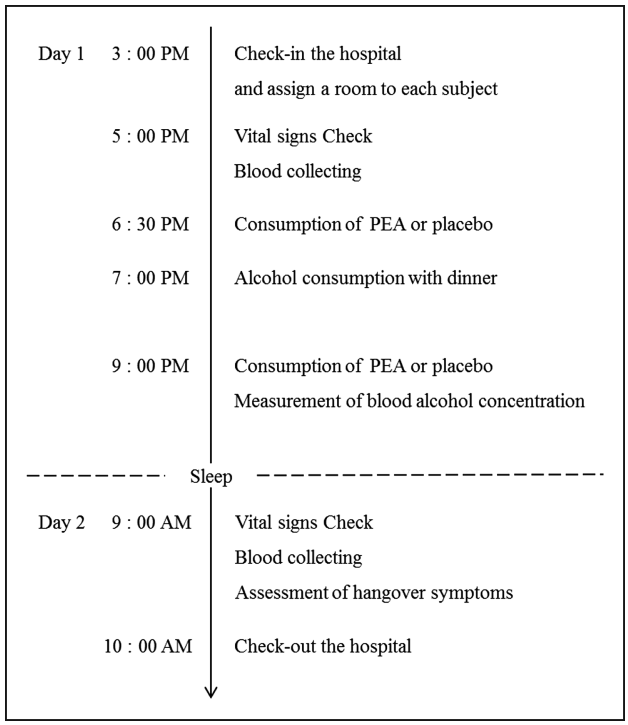

Fig. 2: Time line of study protocol. PEA = polysaccharide-rich extract of *Acanthopanax senticosus.*

resultant polysaccharide-rich extract was freeze-dried to make a PEA powder. Carbohydrate concentration in the fractions was determined using the phenol–sulfuric acid method. Carbohydrate content of the final product was 85%, protein and nuclear acid contamination in the extract was negligible.

4.3. Study design

A randomized, placebo-controlled, double-blind crossover trial was conducted. The timeline of the study protocol is shown in Fig. 3. The study began with baseline measurements of vital signs and collection of blood specimens. After hospitalized, subjects were randomly assigned to receive two bottles of either the extract (n = 14) or placebo (n = 14). All investigators and participants were blinded to the assignment.

The extract was produced by fresh roots of AS using a standard solvent extraction procedure. The prepared placebo had the same color and shape as the extract. Subjects received one bottle of either the extract or placebo and 30 min later they were instructed to consume a prepared meal and 1.75 g of pure alcohol (ethanol concentration of 20%) per kilogram of body weight over 2 h. As soon as they finished alcohol consumption, subjects received another bottle of either the extract or placebo according to their assignment. BAC was measured for 3 h after finishing alcohol consumption. The morning after alcohol consumption, subjects required to complete a survey about the hangover symptoms. Their vital signs were measured and blood tests was conducted the same morning. Subjects then returned to their home with notice of the second phase study. According to the crossover design, subjects received the opposite treatment after a 1-week washout period.

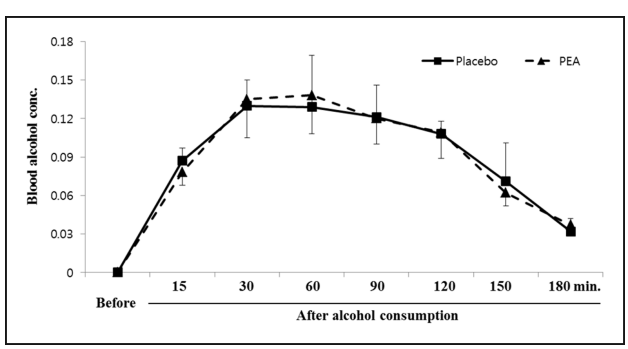

Fig. 3: Blood alcohol concentration (BAC, g%, g/kg body weight) in placebo (solid line) and PEA (dotted line) was measured for 3 h after alcohol consumption. Values are expressed as mean ± SEM. PEA = polysaccharide-rich extract of *Acanthopanax senticosus.*

4.4. Outcome measures

The hangover symptoms were assessed using the Acute Hangover Scale (AHS) answered by subjects in the morning after alcohol consumption ((Bogin et al. 1987; Chauhan and Kulkarni 1991; Kaivola et al. 1983; Khan et al. 1973; Myrsten et al. 1980). The nine AHS items included all the validated items from Rohsenow et al. (2007), and the answer format used the 0–7 scale of Chapman (1970) with Roehrs et al.'s (1991) four anchors: None (0), Mild (1), Moderate (4) and Incapacitating (7). The general instruction was "Please rate how you feel right now on the following rating scales". The mean scores of each symptom and total mean scores were calculated.

In addition to the assessment of the hangover symptoms, changes in vital signs were measured and physiological measurements were conducted by analysis of blood factors [i.e., albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), cortisol, creatinine, C-reactive protein (CRP), gamma glutamyl transferse (GGT), glucose, total bilirubin, total protein, total cholesterol and uric acid.

4.5. Statistical analysis

Statistical evaluation of the experiments was performed by Student's *t*-test or paired *t*-test using SPSS Statistics 17.0 (SPSS Inc., Chicago, IL). All values are expressed as mean ± SD. *P*-values < 0.05 were considered significant.

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