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ORIGINAL RESEARCH

A Novel Blend of Dietary Ingredients Mitigates Blood and Breath Ethanol Levels After Acute Alcohol Intake

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Introduction: Various ingredients have been postulated to attenuate the cognitive and physiological effects of alcohol and next-day hangovers. However, few studies have focused on ingredients that may mitigate the acute effects of alcohol. Thus, the aim of this study was to determine if a novel blend of dietary ingredients would attenuate blood (BAC) and breath (BrAC) ethanol levels after acute alcohol ingestion.

Methods: Thirty-five individuals participated in this double-blind, randomized, crossover clinical trial (#NCT06106620). Participants completed screening and two testing visits. During testing, participants consumed 100mL of alcohol immediately followed by either the supplement blend (SS) or a flavor-matched placebo (PL). BrAC, BAC, and biomarkers related to alcohol metabolism [acetaldehyde, alcohol dehydrogenase, aldehyde dehydrogenase (ALDH)] were made prior to and 30-, 45-, 60-, 90-, 120-, 180-, and 240-min post ingestion, whereas vital signs, urine volume, and subjective mood ratings were made prior to alcohol consumption and 60-, 120-, 180-, and 240-min post.

Results: SS had lower BrAC during the entire post-consumption period ($p \leq 0.05$, d = 0.57–1.07) and lower BAC at 30-, 60-, and 180-min ($p \leq 0.05$) post-consumption vs PL. SS had a lower ($p \leq 0.05$) area under the curve (AUC, d = 0.71) and concentration maximum (Cmax, d = 0.58) for ethanol, and a higher AUC (d = 0.45, d = 0.54, respectively) and Cmax (d = 0.38, d = 0.47, respectively) than PL for acetaldehyde and ALDH levels. Urine output was greater in SS vs PL at 60-min post consumption ($p < 0.001$, d = 1.18). There were more favorable responses for SS vs PL [ie, less head discomfort (d = 0.47), less fatigue (d = 0.59), more energy (d = 0.48), less tiredness (d = 0.41), and better concentration (d = 0.41) (all $p \leq 0.05$)]. There were no differences in nausea and thirst ($p > 0.10$).

Discussion: Overall, SS was effective in reducing BrAC, BAC, and enhancing subjective mood ratings over a 4-hr post alcohol-consumption period vs PL. Thus, SS may mitigate the negative effects induced by acute alcohol intake.

Keywords: alcohol metabolism, antioxidants, acetaldehyde, alcohol dehydrogenase, aldehyde dehydrogenase

Introduction

Alcohol is consumed globally and tends to be principally associated with social events and mealtimes. The total amount of alcohol consumed globally per-capita has increased by 70% from 1990 to 2017, and it is projected to increase another 13% by 2030.[1] In 2017, 47% of adults (globally) were current drinkers, and this is projected to increase to 50% by 2030.[1] It is well known that an acute episode of alcohol consumption in excess can be detrimental to one's physical and mental capabilities, causing negative symptoms such as diminished memory and physical endangerment to self or others.[2,3] A unique blend of dietary ingredients in the form of a liquid supplement [Safety Shot® (SS)] has been developed and produced to theoretically reduce blood alcohol content. SS includes a collection of ingredients with antioxidant activity [red ginseng, N-acetyl cysteine (NAC), Dandelion extract, *Mucuna pruriens*, Citicoline, and milk thistle], anti-inflammatory activity (milk thistle, dandelion extract, apple pectin, theacrine, and ginseng), and nootropic effects [(caffeine anhydrous, Cognizin® Citicoline, Methylliberine (Dynamine®), and Theacrine (TeaCrine®)].

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Most alcohol is metabolized in hepatocytes via alcohol dehydrogenase (ADH) which converts ethanol to acetaldehyde, which is further converted into acetate via aldehyde dehydrogenase (ALDH).[2] When ethanol arrives in the liver in overabundance (as in the case of binge drinking), the microsomal ethanol oxidizing system (MEOS) aids metabolism because alcohol dehydrogenase becomes saturated.[2] Within the MEOS cytochrome P450 E1 (CYP2E1) converts ethanol to acetaldehyde and ALDH subsequently converts acetaldehyde into acetate.[2] These reactions produce high levels of co-factors ($NADP^+$ and NADH) which then lead to the formation of reactive oxygen species (ROS) and in turn causes disruptions/imbalances in cellular metabolism as in the case of acute binge drinking.[4] Excessive drinking can decrease the levels of multiple antioxidant enzymes [such as glutathione (GSH) and glutathione peroxidase (GPX)] and produce a vast amount of oxidative stress, which can subsequently lead to tissue injury.[5,6] In fact, acetaldehyde (formed from the metabolism of ethanol in the brain) can react with other endogenous bioactive compounds (such as proteins to form neurotoxic adducts involved in producing oxidative stress.[7] In addition to oxidative stress and acetaldehyde adduct formation, tissue injury may also occur through a variety of other mechanisms such as inflammation, intestinal barrier integrity disruption, decreased anabolic signaling, enhanced catabolic processes, profibrotic changes, mitochondrial dysfunction and injury, and cell membrane perturbations.[8] As oxidative stress increases, so too does the progression of lipid peroxidation, and both of these processes have been shown to decrease the activity of ALDH. This leads to a reduced clearance of acetaldehyde and subsequently the development of hangover symptoms in drinkers.[9,10] Thus, it may be advantageous to limit oxidative stress and lipid peroxidation while increasing the activity of ALDH and increasing the clearance of acetaldehyde.

Alcohol is mainly absorbed by the upper GI tract by diffusion, promoting inflammation, which may potentially contribute to organ failure in the context of prolonged, chronic drinking.[3] Alcohol consumption is also associated with increased levels of pro-inflammatory cytokines in the blood (ie, IL-6, IL-10, IL-12, IFN-γ, and TNF-α) and reduced antioxidants [GSH and superoxide dismutase (SOD) concentrations].[11] The gut mucosa is particularly susceptible to alcohol-induced injury because alcohol and its metabolites directly damage epithelial cells through generation of ROS and the disruption of tight junction protein expression and signaling, resulting in a loss of intestinal barrier function, creating the possibility of bacterial endotoxins entering the circulation.[12,13] Ultimately, brain exposure to ethanol and/or its metabolites may trigger and determine the intensity of hangover symptoms. Since the elimination rate of alcohol plays a critical role in the presence and severity of a hangover, it would be favorable to increase the enzymatic conversion of ethanol to acetaldehyde prior to reaching the brain because ethanol crosses the blood–brain barrier, whereas acetaldehyde mostly does not.[2] Thus, SS may theoretically preserve antioxidant status, reduce inflammation, and increase ADH and ALDH activity, leading to increased clearance of acetaldehyde and a reduction in the amount of ethanol that reaches the brain.

Previous investigations have examined the impact of various single bioactive food compounds on breath alcohol concentration (BrAC) and hangover severity/symptoms in animals[5,14–16] and humans.[17–19] However, most of these prior studies have had a primary focus of a single ingredient/intervention on mitigating hangover symptoms rather than examining the effects from a combination of ingredients. Readers are referred to reviews on medical interventions and bioactive food compounds that may mitigate ethanol-induced injuries and hangover symptoms.[3,20] For example, Kim et al[17] measured the impact of a fruit extract (*Hovenia dulcis*) on alleviating hangover symptoms after ingesting 360 mL of 17.5% alcohol and found that the extract promoted a significant suppression of hangover symptoms in men. Lv et al[19] conducted an investigation in men and women while using hydrogen gas inhalation followed by 100 mL of 40% alcohol, and then 350 mL of hydrogen-infused water and found a reduction in hangover symptoms score and severity (ie, fewer headaches and mitigated excessive sweating 24hr post alcohol consumption in men and women) and BrAC at 30-, 60-, and 90-min post ingestion vs placebo (PL) in men only. One previous study investigated the acute impact of alcohol ingestion with red ginseng. Lee et al[18] measured the impact of red ginseng on blood alcohol levels (BAC) and BrAC in men after consuming 100 mL of 40% alcohol and observed an attenuation of BAC and BrAC at 30-, 45-, and 60-min post as compared to a PL. However, the authors acknowledged their limitations in not measuring key enzymes within alcohol metabolism (ie, ADH and ALDH). Although these studies indicate that certain individual food bioactives reduce BAC and BrAC while also mitigating the effects of hangover symptoms and severity following alcohol consumption, there is

a dearth of data examining BAC and BrAC in conjunction with biomarkers of alcohol metabolism and key regulatory enzymes.

Thus, the aim of this study was to determine if an over-the-counter blend of dietary ingredients (SS) could acutely mitigate blood and breath ethanol content while also affecting blood biomarkers and key enzymes indicative of accelerated alcohol metabolism. Based on pilot data, the existing literature, and the antioxidant and anti-inflammatory capacity of the ingredients in SS, we hypothesized that SS would lower BAC and BrAC following acute alcohol consumption by slowing absorption, accelerating alcohol metabolism (ie, affecting acetaldehyde) and clearance, and upregulating key enzymes (eg, alcohol dehydrogenase and/or aldehyde dehydrogenase). Additionally, we hypothesized that SS would promote improved feelings of affect following acute alcohol consumption (eg, energy, fatigue, head discomfort, tiredness, concentration, nausea, and thirst).

Materials and Methods

Experimental Design

This was a double-blind (neither the participants nor the researchers had prior knowledge of the assigned treatments), randomized, two-arm, placebo-controlled, within-subject crossover trial in which participants visited the laboratory on three occasions (one screening visit and two testing visits). This study was conducted according to the guidelines outlined in the Declaration of Helsinki of 1975, and all procedures involving human subjects were approved by the Advarra IRB on 12/7/23 (Pro00075972). Written informed consent was obtained from all subjects prior to enrollment, and the data was collected from January to April of 2024. The study was pre-registered on clinicaltrials.gov (#NCT06106620). This study was conducted at the Center for Applied Health Sciences, a contract research organization located in Northeast Ohio where participants were locally recruited. During the initial screening visit, each participant's medical history and blood work [Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Gamma-Glutamyl Transferase (GGT), and lipid panel] were assessed to ensure they were within acceptable clinical ranges, and their 24-hour dietary recall was evaluated. Once participants were deemed eligible for the study, they were randomly assigned to receive either treatment first in a counterbalanced design. During the testing visits (visits 2 and 3, which were spaced at least 7 days apart), participants completed all baseline assessments before consuming 100 mL (~3.4 oz) of 40% alcohol (Ketel One® vodka) along with a standard serving (21g) of Colby Jack Cheese (Great Value, Walmart Inc). Participants were given a five-minute period to consume their assigned product and serving of cheese. Participants were then given 10 minutes to drink either a liquid blend of dietary supplements (Safety Shot®, Jupiter, Florida) or a flavor- and volume-matched placebo. Assessments included breath alcohol content (BrAC), serum blood alcohol levels (BAC), serum blood alcohol dehydrogenase levels (ADH), serum acetaldehyde levels, and serum aldehyde dehydrogenase (ALDH) levels at baseline (prior to ingestion), and 30-, 45-, 60-, 90-, 120-, 180-, 240-min post ingestion, as well as subjective feelings of affect (headache, nausea, fatigue, energy, tiredness, thirst, and concentration), urine volume, and vital signs (prior to ingestion), and 60-, 120-, 180–240-min post-ingestion. See Figure 1 for a study design overview.

Participants

Thirty-five healthy men and women participated, and 34 completed both testing visits (see Table 1 for participant characteristics). Potential participants were deemed eligible if they were in good health as determined by medical history and safety screening blood work (CBC, CMP, GGT, and lipid panel) and of non-Asian descent, between the ages of 21 and 55 years, had a body mass index (BMI) of 18.5–34.9 kg•m^{-2}, weighed a minimum of 135 lbs (~61.3kg), did not exhibit moderate-to-severe hypertension (ie, resting SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg), possessed a resting heart rate ≤90 bpm, and consumed alcohol socially (consumption limits defined in the following sentences). Prior to participation, all participants indicated their willingness to comply with all aspects of the experimental and supplement protocol. Participants were excluded if they: (a) had a history of diabetes or pre-diabetes or any endocrine disorder, hepatorenal, musculoskeletal, autoimmune, or neurologic disease; (b) had a history of malignancy in the previous 5 years except for non-melanoma skin cancer (basal cell cancer or squamous cell cancer of the skin); (c) had prior gastro-intestinal bypass surgery; (d) had medical diagnoses of gastrointestinal or metabolic diseases that might impact nutrient

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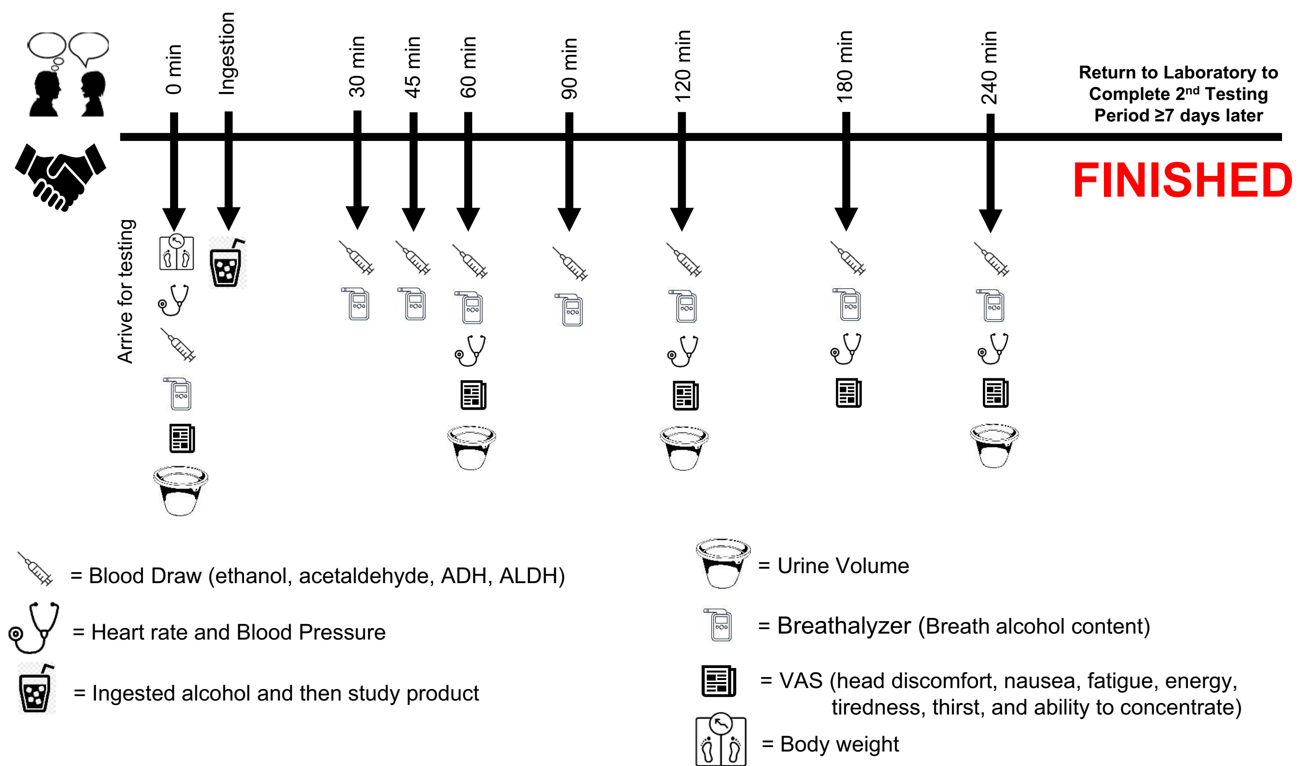

Figure 1 Study design overview.
Notes: ADH: Alcohol dehydrogenase; ALDH: Aldehyde dehydrogenase.

absorption or metabolism (eg short bowel syndrome, diarrheal illnesses, history of colon resection, gastroparesis, or Inborn-Errors-of-Metabolism); (e) had medically diagnosed chronic inflammatory conditions or diseases (eg, rheumatoid arthritis, Crohn's Disease, ulcerative colitis, lupus, or HIV/AIDS); (f) had previous medical diagnoses of asthma, gout, or

Table 1 Baseline Study Participant Descriptive Characteristics

Variable	Total (n=35)	Placebo (PL) first (n=18)	Safety shot (SS) first (n=17)	p-value
Age	36.31 (9.13)	39.67 (8.83)	32.76 (8.26)	**0.023**
Sex, n female (%)	17 (48.6%)	11 (64.7%)	6 (35.3%)	0.181
SBP (mmHg)	120.86 (12.42)	118.83 (13.15)	123.00 (11.59)	0.328
DBP (mmHg)	76.43 (8.77)	75.94 (7.91)	76.94 (9.83)	0.742
HR (bpm)	67.51 (9.32)	67.89 (9.00)	67.12 (9.91)	0.811
BMI	27.45 (3.50)	27.30 (3.48)	27.62 (3.62)	0.793
Weight (kg)	81.65 (13.93)	79.95 (11.91)	83.45 (15.97)	0.465
Height (in)	67.71 (3.60)	67.03 (2.60)	68.42 (4.38)	0.257
Height (cm)	171.97 (9.13)	170.26 (6.62)	173.79 (11.12)	0.257
Body Fat (%)	24.87 (11.09)	27.37 (9.26)	22.38 (12.44)	0.194

Notes: Groups represent which protocol was done first (at visit 2) and were compared using the *t*-test and Fisher's exact test. P-values in bold are significant (p≤0.05). Results presented as mean (SD).
Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; BMI, Body Mass Index.

fibromyalgia; (g) had history of unstable or new onset cardiovascular, liver, renal, or thyroid disease or current use of thyroid, hyperlipidemic, hypoglycemic, anti-hypertensive, or anti-coagulant medication/s; (h) were currently pregnant or were ≤120 days postpartum or nursing; (i) were current smokers, nicotine users, or discontinued smoking within one month of enrollment, (j) had a known allergy to any of the ingredients in the supplement or the placebo; (k) had currently been participating in another research study with an investigational product or have been in another research study in the past 30 days; (l) used corticosteroids or testosterone replacement therapy (ingestion, injection, or transdermal); (m) possessed a history of or recent treatment for alcohol ingestion or history of drug/alcohol dependence/abuse; (n) were excessive consumers of alcohol (>2 drinks per day or >10 drinks per week); (o) possessed fasting blood sugar >125 mg/dL; (p) had any other diseases or conditions that, in the opinion of the medical staff, could confound primary endpoints or place the participant at increased risk of harm if they were to participate; or (q) did not demonstrate a verbal understanding of the informed consent document.

Participants were free to eat as they chose and exercise as they pleased but instructed to maintain their normal dietary and physical activity patterns throughout their period of enrollment in the study. Participants were required to complete a 24-hour diet record prior to arriving at the laboratory for their initial screening visit. Participants were given a copy of this dietary record and instructed to duplicate that diet (ie, all food and liquids) 24 hours prior to each subsequent laboratory visit. Prior to each subsequent visit, participants were asked to verbally confirm their previous day's 24-hour diet adherence. In addition, the participants were required to refrain from exercise and alcohol for 48 hours, avoid caffeine for 24 hours, and arrive fasted for 10 hours. All compliance with these requirements was verbally confirmed by each participant at the beginning of each study visit. All participants were 100% compliant with these requirements.

Anthropometric Parameters, Blood Pressure, and Blood and Urine Assessments

Standing height was determined using a wall-mounted stadiometer and body weight (BW) was measured using a Seca 767TM Medical Scale; note, body weight was measured at each visit. Percent body fat was assessed on the first visit with an InBody 570 (InBody USA, Cerritos, CA). Seated resting heart rate (HR) and blood pressure (SBP and DBP) were measured using an automated blood pressure cuff (Omron HEM-780) prior to alcohol ingestion, and 60-, 120-, 180-, and 240-min post alcohol + supplement ingestion during testing visits 2 and 3. Urine volume was measured using a 60 mL syringe and was collected prior to alcohol ingestion and 60-, 120-, 180-, and 240-min post alcohol + supplement ingestion during testing visits 2 and 3. Urine-specific gravity (USG) was measured prior to alcohol ingestion via a handheld refractometer (Atago, PAL-10S) to ensure consistent hydration levels between visits 2 and 3.

Visual-Analog Scales (VAS)

One hundred-millimeter anchored VAS were completed before, and 60-, 120-, 180-, and 240-min post alcohol + supplement ingestion on testing visits 2 and 3. VAS assessed subjective ratings of head discomfort (headache), nausea, fatigue, energy, tiredness, thirst, and ability to concentrate and were anchored with "No Nausea", "Lowest possible", "No Energy", or "Extremely Tired" and "Very Nauseated", "Highest possible", "Highly Energetic", or "Wide awake". The validity and reliability of VAS in assessing similar subjective constructs have been previously established[21] and reported.[22,23]

Plasma Alcohol (BAC), Acetaldehyde Concentrations (AD), Alcohol Dehydrogenase (ADH), Aldehyde Dehydrogenase (ALDH), and Alcohol Levels of Expiratory Air (BrAC)

Venous catheters (McKesson, Richmond, VA, USA) were placed in participants' antecubital veins by a research nurse prior to alcohol + supplement ingestion during testing visits 2 and 3. During each sampling time point (prior to alcohol ingestion, and 30-, 45-, 60-, 90-, 120-, 180-, and 240-min post alcohol + supplement ingestion) venous blood (~8.5mL) was collected in serum separator tubes (SST) tubes (Becton, Dickinson, and Company Franklin Lakes, NJ, USA) for determination of serum ethanol, acetaldehyde, alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH) concentrations. Blood samples were then allowed to sit at room temperature for 30 minutes to promote clotting and

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subsequently centrifuged at 1600 g for at least 10 min using a desktop centrifuge (Dexter 642E). Following centrifugation, serum was aliquoted into 3 mL cryogenic storage tubes and immediately stored at −80°C until shipped on dry ice to Auburn University for subcontracted analyses described in the following paragraphs. Notably, cryogenic storage tubes were labelled with participant and visit codes to maintain blinding for Auburn University technicians.

Upon receipt of samples on dry ice, Auburn University technicians immediately placed cryotubes in −80°C freezers until assays were performed. Commercially available enzymatic ethanol assays (BioAssay Systems, EnzyChrom™ Ethanol Assay Kit catalog #ECET-100), acetaldehyde assays (Abnova catalog #KA6206), and ADH assays (Sigma-Aldrich catalog #MAK498) were used to obtain relative concentrations or activity levels on undiluted serum strictly according to manufacturer's instructions. A commercially available enzymatic ALDH assay (Sigma-Aldrich catalog #MAK082) was used to obtain activity levels on 4x-diluted serum strictly according to manufacturer's instructions. A BioTek Synergy H1 hybrid spectrophotometer (Agilent) was used to obtain absorbance readings for all assays. Given the high number of participants and blood sampling time points, 14 plates were run per target ensuring that each participant's visit 2 and 3 serum samples were contained on the same plate. Kit-to-kit (inter-plate) coefficient of variation values were approximately 6.6% for ethanol assays, 6.6% for acetaldehyde assays, 18.6% for ADH assays, and 10.4% for ALDH assays.

Expiratory air BrAC was assessed prior to alcohol ingestion, and 30-, 45-, 60-, 90-, 120-, 180-, and 240-min post alcohol + supplementation during testing visits 2 and 3, with a DOT-approved BACtrack® S80 Breathalyzer. This test involved participants breathing in the device for several seconds until the device beeped to signal the reading was obtained. Additionally, duplicate readings were obtained if there were any errors.

Alcohol Ingestion and Supplement Protocol

After baseline samplings [ie, pre-consumption USG, BrAC, venous blood draw (BAC, AD, ADH, ALDH), VAS, vitals, urine volume, and body weight] participants ingested their alcohol and cheese immediately prior to study product ingestion. The study products were prepared in the form of a 12 fl. oz beverage for oral ingestion and provided in generic containers labeled "A" and "B" with similar colors for administration. Participants orally ingested a placebo (PL: flavor-matched water) or a blend of dietary supplements (SS: Safety Shot®, see SFP Figure 2). Using a Latin Square cross-over design, participants were randomly assigned to receive the study beverages in a specific counterbalanced order such that approximately one-half received PL, while the other half received SS during their first study visit (ie, visit 2). The alcohol and study products were ingested in the laboratory in the presence of the research staff. Visit 2 and visit 3 trials were no less than seven days apart. All the test products were made in an NSF-certified facility with GMP at DryBev, Inc. [Dallas (Farmers Branch), TX].

Statistical Analyses

The first paragraph in this section describes statistical analyses performed by CAHS researchers for all non-blood-related variables. The paragraph that follows describes statistical analyses performed by Auburn University researchers on blood-related variables. The sample size was determined based on Lee et al[18] observing a moderate effect on BAC, and ensuring high statistical power. An a priori power analyses revealed that a minimum sample size of 16 was needed to achieve 80% power. Unblinding of the assigned treatments was done by the sponsor after all statistical analyses were conducted.

Baseline characteristics were compared between participants who received PL first vs those who received SS first. Statistical significance was determined using t-tests and Fisher's exact test. Paired samples t-tests were used to compare characteristics between study arms (PL vs SS). Repeated measures of the primary outcome measures were reported at each timepoint and compared using paired t-tests. Linear mixed-effect models with random intercept adjusted for age and sex per subject were fitted to the data to explore within time-point main effects of trial (PL vs SS). Subsequently, age and sex-adjusted linear mixed-effect models with random intercept and slope for subjects nested within trial was conducted to further explore the main effects of time and trial, as well as interaction effects of time x trial. This interaction term allowed us to assess whether the trials had differing effects over time on the outcome measures (eg, BrAC, urine output, VAS outcomes, vitals). Area under the curve (AUC) was calculated using the trapezoidal method for each outcome

Nutrition Facts

Serving Size: 1 Can 12oz (355mL)

Amount per serving	
Calories	**10**
	% Daily Value*
Total Fat 0g	0%
Saturated Fat 0g	0%
Trans Fat 0g	0%
Cholesterol 0mg	0%
Sodium 200mg	9%
Total Carbohydrates 0g	0%
Dietary Fiber 0g	0%
Total Sugars 0g	0%
Includes 0g Added Sugars	0%
Protein 0g	
Vitamin B1(as Thiamine) 2.4mg	200%
Vitamin B2 (Riboflavin) 2.6mg	200%
Vitamin B3 (as Niacin) 25mg	160%
Vitamin B6 (as Pyridoxine & Pyridoxal 5 Phosphate) 3.4mg	200%
Vitamin B12 (as Methylcobalamin) 2.4mg	200%
Vitamin B5 (as Pantothenic Acid) 10mg	200%
Calcium (as Calcium Citrate) 50mg	4%
Magnesium (as Magnesium Citrate) 50mg	12%
Potassium (as Potassium Chloride) 50mg	1%
Choline 27mg	5%

Not a significant source of calories from fat, saturated fat, trans fat, cholesterol, dietary fiber, vitamin A, vitamin D, and iron.

% Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

SHAKE WELL

Ingredients: Triple Filtered Purified Water, Apple Extract, Natural Flavors, N-acetyl Cysteine, Citric Acid, Sodium Citrate, N-acetyl Tyrosine, Taurine, Milk Thistle, Dandelion Extract, Glycine, Sucralose, Calcium Citrate, Mucuna Pruriens, Cognizin® Citicoline, Caffeine Anhydrous, Phenylalanine, Theobromine, Potassium Sorbate (preserve freshness), Magnesium Citrate, Sodium Benzoate (preserve freshness), Potassium Chloride, Panax Ginseng, Synephrine HCL, Methylliberine (as Dynamine®), Theacrine (as TeaCrine®), Vitamin B5 (Pantothenic Acid), Vitamin B1 (Thiamine), Vitamin B2 (Riboflavin), Vitamin B6 (Pyridoxal 5 Phosphate and Pyridoxine HCL), Vitamin B12 (Methylcobalamin)

Figure 2 Supplement Facts Panel for Safety Shot®.

measure, and paired t-tests were used to compare mean AUCs between the two treatments. Normality was assessed using Q–Q plot and Shapiro–Wilks test. Severe non-normal measures were normalized using Box-Cox transformation or analyzed with non-parametric methods. Effect sizes, accounting for repeated measures, are reported as Cohen's d (with

0.2 considered a small effect, 0.5 considered a medium effect, and 0.8 considered a large effect) and Phi coefficient. P-values <0.05 were considered significant and p-values <0.10 were considered trends indicating a possible difference between trials or over time. Statistical analyses were conducted using SPSS 28.0 (IBM Corp). A chi-square goodness-of-fit test was used to assess differences in proportions of adverse events between treatments.

Serum ethanol concentrations (BAC), serum markers of metabolism (acetaldehyde), and key regulatory enzymes (ADH and ALDH) over time between trials were analyzed using a mixed effects factorial ANOVA in GraphPad Prism v.10.0. Manual Bonferroni post hocs were applied if significant interactions were observed, which involved dividing p <0.05 by 8 time points and adjusting statistical significance to p <0.007. Paired samples t-tests for PL vs SS Cmax and AUC (trapezoid method) comparisons were performed using Jamovi 2.3.28. Similar to CAHS statistical analyses, p-values <0.05 for Cmax and AUC were considered significant and p-values <0.10 were considered trends indicating a possible difference between trials or over time.

Results

Demographic & Baseline Characteristics

Thirty-five participants were recruited (17 women, 18 men, with a mean age of 36.3 ± 9.1yr). At the screening visit, the participants that had PL first vs SS first did not differ on demographic or hematological measurements (p > 0.05), except for age (39.67 ± 8.83 vs 32.76 ± 8.26 yr, p = 0.023) and chloride (104.06 ±1.31 vs 102.88 ± 1.83 mmol/L, p = 0.036), see Tables 1 and 2.

Table 2 Blood Chemistries at Screening Baseline Visit

Variable	Total (n=35)	Placebo (PL) first (n=18)	Safety shot (SS) first (n=17)	p-value
WBC (x10E3/uL)	5.59 (1.65)	5.97 (1.45)	5.18 (1.79)	0.159
RBC (x10E6/uL)	4.85 (0.52)	4.74 (0.48)	4.96 (0.55)	0.203
Hemoglobin (g/dL)	14.46 (1.59)	14.13 (1.85)	14.82 (1.21)	0.203
Hematocrit (%)	42.84 (4.09)	41.98 (4.49)	43.75 (3.52)	0.206
Glucose (mg/dL)	91.60 (7.39)	91.44 (6.67)	91.76 (8.29)	0.900
BUN (mg/dL)	13.89 (3.76)	12.83 (3.52)	15.00 (3.78)	*0.088*
Creatinine (mg/dL)	0.92 (0.16)	0.90 (0.16)	0.95 (0.16)	0.345
eGFR (mL/min/1.73)	97.51 (11.63)	95.67 (11.14)	99.47 (12.15)	0.341
BUN/Crea ratio	15.17 (3.70)	14.50 (3.59)	15.88 (3.79)	0.275
Sodium (mmol/L)	140.06 (1.86)	140.33 (1.75)	139.76 (1.99)	0.374
Potassium (mmol/L)	4.32 (0.24)	4.30 (0.26)	4.35 (0.23)	0.572
Chloride (mmol/L)	103.49 (1.67)	104.06 (1.31)	102.88 (1.83)	**0.036**
CO_2 (mmol/L)	23.00 (1.86)	23.33 (1.91)	22.65 (1.80)	0.283
Calcium (mg/dL)	9.44 (0.34)	9.37 (0.35)	9.51 (0.32)	0.247
Total Protein (g/dL)	7.04 (0.32)	7.05 (0.32)	7.03 (0.33)	0.852
Albumin (g/dL)	4.61 (0.19)	4.57 (0.16)	4.65 (0.20)	0.204
Globulin (g/dL)	2.43 (0.30)	2.48 (0.27)	2.38 (0.32)	0.318

(*Continued*)

Table 2 (Continued).

Variable	Total (n=35)	Placebo (PL) first (n=18)	Safety shot (SS) first (n=17)	p-value
A/G ratio	1.92 (0.26)	1.86 (0.22)	1.99 (0.29)	0.151
Bilirubin (mg/dL)*	0.62 (0.29)	0.57 (0.26)	0.67 (0.32)	0.267
ALK Phos (IU/L)	66.49 (21.32)	66.61 (23.59)	66.35 (19.36)	0.972
AST (IU/L)*	23.54 (8.79)	21.06 (4.86)	26.18 (11.18)	0.152
ALT (IU/L)	23.26 (11.45)	22.17 (9.06)	24.41 (13.74)	0.570
Total Chol (mg/dL)	192.23 (40.86)	198.39 (39.49)	185.71 (42.45)	0.366
Triglyceride (mg/dL)*	94.94 (51.23)	95.72 (58.81)	94.12 (43.58)	0.832
HDL (mg/dL)	57.80 (17.30)	59.89 (19.57)	55.59 (14.79)	0.470
VLDL (mg/dL)*	17.57 (8.65)	17.61 (10.04)	17.53 (7.20)	0.753
LDL (mg/dL)	116.86 (36.31)	120.89 (37.30)	112.59 (35.85)	0.507
LDL/HDL (mg/dL)	2.20 (0.89)	2.22 (0.85)	2.18 (0.96)	0.897
Total/HDL Ratio	3.55 (1.07)	3.56 (1.06)	3.53 (1.12)	0.923
GGT (IU/L)*	16.66 (9.20)	15.56 (6.87)	17.82 (11.26)	0.556

Notes: *log-transformed due to skewness. Groups represent which protocol was done first (at visit 2) and were compared using the *t*-test. P-values in bold are significant ($p \leq 0.05$), whereas p-values in italics are trends ($p \leq 0.10$). Results presented as mean (SD).
Abbreviations: WBC, White Blood Cells; RBC, Red Blood Cells; BUN, Blood Urea Nitrogen; eGFR, estimated Glomerular Filtration Rate; A/G ratio, Albumin/Globulin ratio; ALK Phos, Alkaline Phosphatase; AST, Aspartate Aminotransferase; ALT, alanine transaminase; GGT, Gamma-Glutamyl Transferase.

Physiological Measurements

BrAC levels were significantly lower in SS compared to PL at all time points from 30 to 240 min ($p < 0.001$ to $p = 0.002$, Table 3), as well as overall (main effect of trial: $\beta = 0.004$, SE = 0.002, $p < 0.001$) and across time (interaction: $\beta =$

Table 3 Breath Alcohol Concentrations Over Time (BrAC) and Area Under the Curve (AUC)

Time (min)	Placebo (PL)	Safety Shot (SS)	Delta PL - SS	p-value	Cohen's *d*
0	0	0	–	–	–
30	0.0548 (0.0135)	0.0440 (0.0128)	0.0107 (0.0100)	**<0.001**	1.07
45	0.0546 (0.0124)	0.0461 (0.0129)	0.0086 (0.0086)	**<0.001**	1.00
60	0.0509 (0.0126)	0.0456 (0.0129)	0.0054 (0.0082)	**<0.001**	0.65
90	0.0428 (0.0127)	0.0392 (0.0124)	0.0036 (0.0058)	**<0.001**	0.62
120	0.0342 (0.0119)	0.0307 (0.0106)	0.0036 (0.0048)	**<0.001**	0.75
180	0.0216 (0.0112)	0.0187 (0.0102)	0.0029 (0.0050)	**0.002**	0.57
240	0.0113 (0.0101)	0.0081 (0.0089)	0.0032 (0.0050)	**<0.001**	0.65
AUC	7.71 (2.48)	6.66 (2.27)	1.05 (0.90)	**<0.001**	1.17

Notes: P-values represent the within-time main effect between the placebo and safety shot trials, adjusted for the effects of age and sex, accounting for repeated measures. P-values in bold are significant ($p \leq 0.05$). Results presented as mean (SD). Cohen's d: 0.2=small, 0.5=medium, 0.8=large effect size.

−0.000029, SE = 0.000008, p < 0.001, Table 3), indicating that SS significantly lowered BrAC levels. The AUC was significantly lower in SS for BrAC (p < 0.001) (Table 3).

Markers of Alcohol Metabolism and Key Enzymes

Blood ethanol concentrations revealed a significant interaction (p = 0.013), a significant main effect of time (p < 0.001), and a trend for a group effect (p = 0.096). Post hoc analyses revealed that PL BAC was significantly greater than SS at 30 min (p = 0.002), 60 min (p = 0.003), and 180 min (p < 0.001). Over time, 30–240 min BAC values were significantly greater than 0 min values (p < 0.001). The AUC for blood ethanol was 12.3% lower in SS vs PL (p < 0.001, d = 0.71) and the Cmax was 14.8% lower in SS vs PL (p = 0.002, d = 0.58) (See Figure 3). Serum acetaldehyde revealed a significant main effect of time (p < 0.001), but not group (p = 0.375) or group × time (p = 0.176). Over time, the serum acetaldehyde values from 45 to 240 min were significantly greater than the 0- and 30-min values (p < 0.05). The AUC and Cmax for acetaldehyde were both significantly higher in SS vs PL (p = 0.014, d = 0.45 and p = 0.039, d = 0.38 respectively), (See Figure 4). Serum alcohol dehydrogenase revealed a significant main effect of time (p < 0.001), but not group (p = 0.879) or group × time (p = 0.427). Over time, alcohol dehydrogenase values from 45 to 240 min were significantly greater than 0 min values. Additionally, there was no difference in AUC (p = 0.331) or Cmax (p = 0.121) for alcohol dehydrogenase (See Figure 5). Serum aldehyde dehydrogenase revealed a significant main effect of time (p < 0.001), but not group (p = 0.134) or group × time (p = 0.345). Over time, the aldehyde dehydrogenase values from 30 to 240 min were significantly greater than the 0 min values. The AUC and Cmax for aldehyde dehydrogenase were both significantly greater in SS vs PL (p = 0.004, d = 0.54 and p = 0.010, d = 0.47 respectively), (See Figure 6).

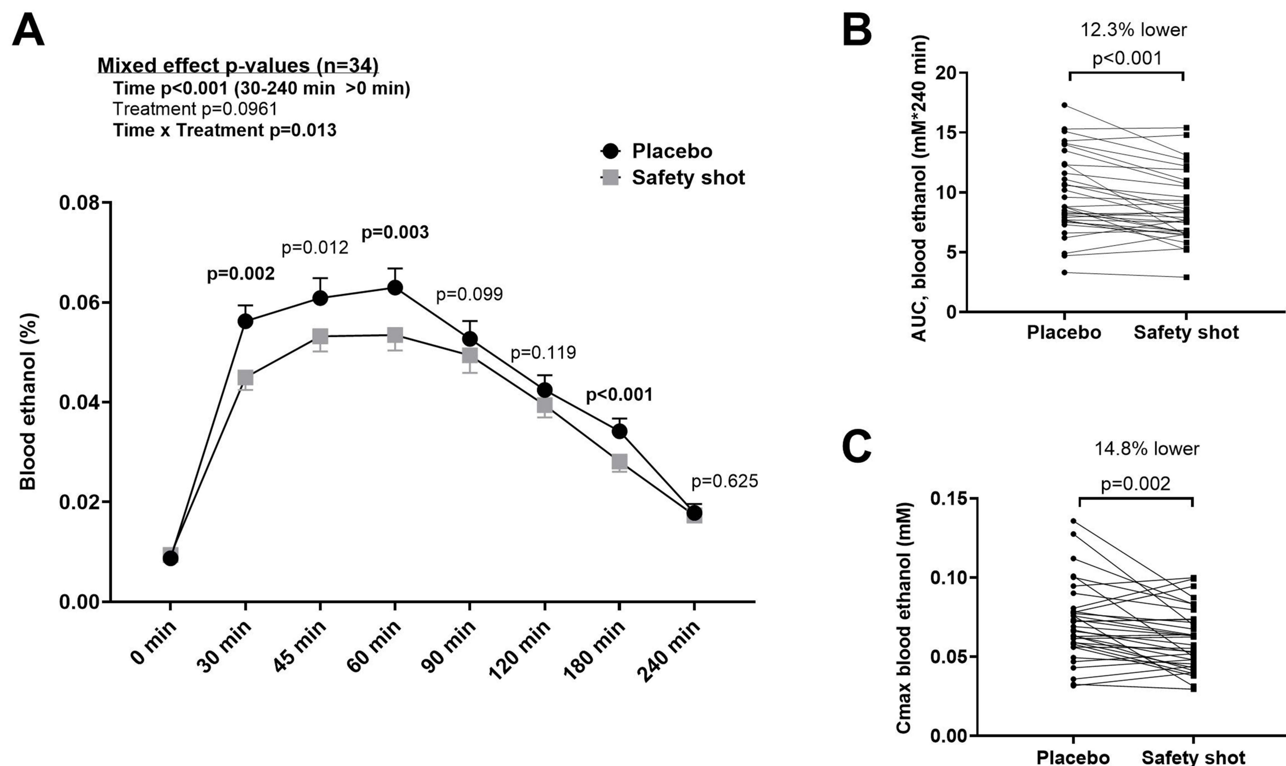

Figure 3 Serum ethanol outcomes.

Notes: Data presented as means ± SEM values. Significance at each time point (bolded) accepted as p<0.007 due to 8 comparisons. Serum ethanol concentrations over time between trials (**A**), area under curve (AUC) values between trials (**B**), and maximal concentration (Cmax) values between trials (**C**). For panel A, model main and interaction effects are presented, and bold values indicate statistical significance. Other statistical notes are presented in figure panels.

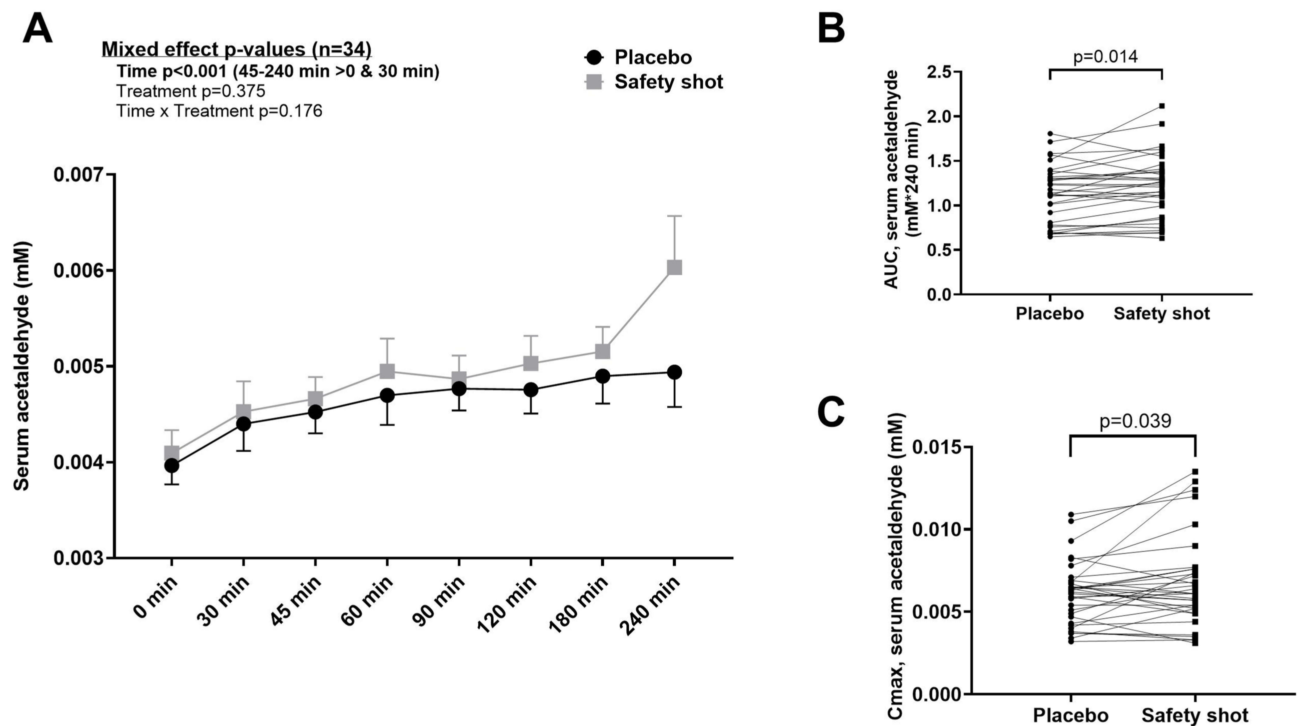

Figure 4 Serum acetaldehyde outcomes. Data presented as means ± SEM values.

Notes: Serum acetaldehyde concentrations over time between trials (**A**), area under curve (AUC) values between trials (**B**), and maximal concentration (Cmax) values between trials (**C**). For panel A, model main and interaction effects are presented, and bold values indicate statistical significance. Other statistical notes are presented in figure panels.

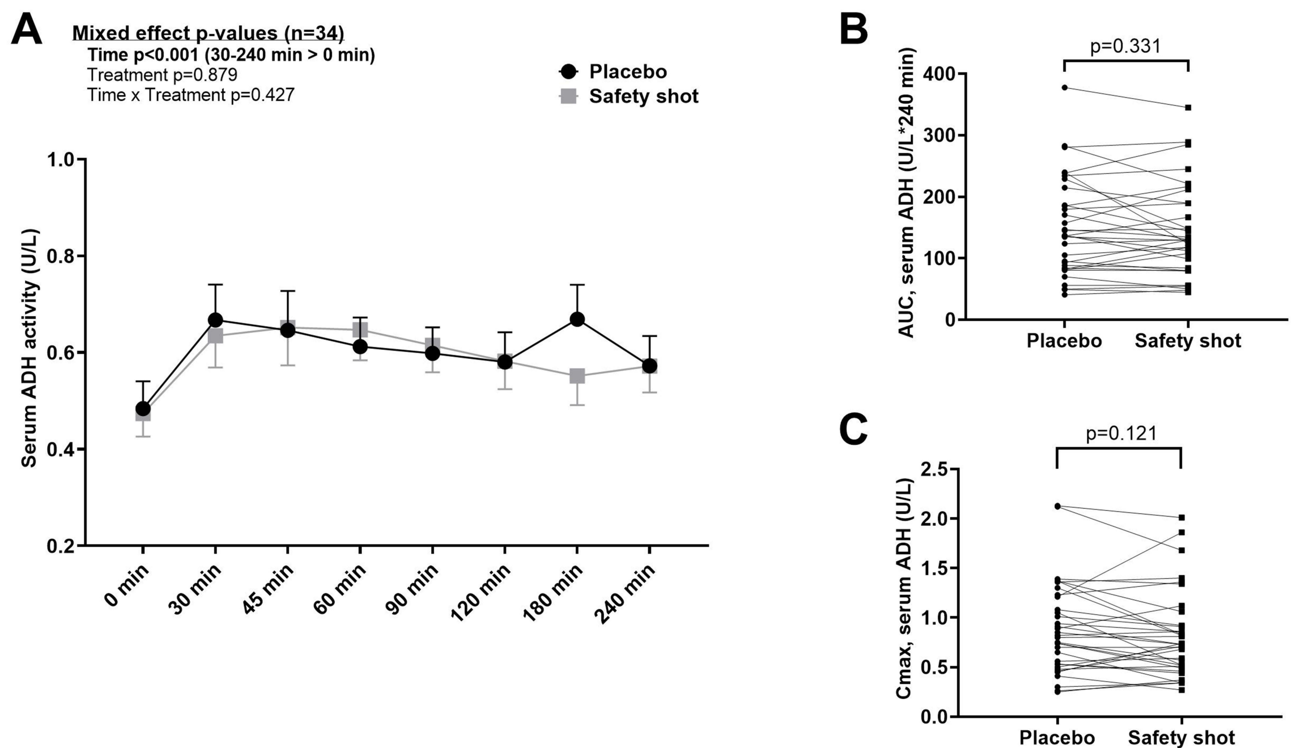

Figure 5 Serum alcohol dehydrogenase (ADH) outcomes. Data presented as means ± SEM values.

Notes: Serum alcohol dehydrogenase outcomes over time between trials (**A**), area under curve (AUC) values between trials (**B**), and maximal concentration (Cmax) values between trials (**C**). For panel A, model main and interaction effects are presented, and bold values indicate statistical significance. Other statistical notes are presented in figure panels.

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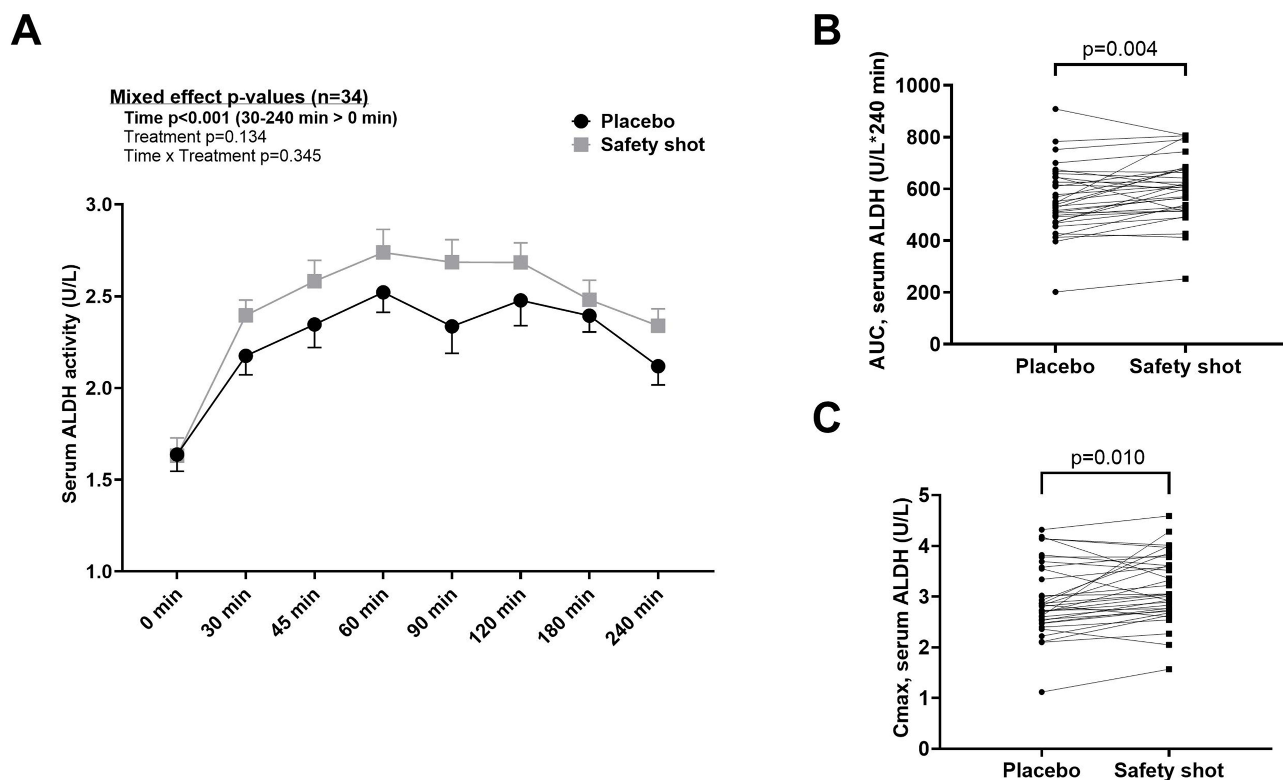

Figure 6 Serum aldehyde dehydrogenase outcomes. Data presented as means ± SEM values.

Notes: Serum aldehyde dehydrogenase (ALDH) outcomes over time between trials (**A**), area under curve (AUC) values between trials (**B**), and maximal concentration (Cmax) values between trials (**C**). For panel A, model main and interaction effects are presented, and bold values indicate statistical significance. Other statistical notes are presented in figure panels.

Visual-Analog Scales (VAS) and Urine Output

Subjective (perceived) head discomfort ratings were significantly lower in SS (vs PL) at 60 min (1.0 ± 1.1 vs 0.8 ± 1.2 cm, p = 0.022) and 240 min (2.0 ± 2.3 vs 0.8 ± 1.2 cm, p = 0.003). No differences were found for nausea or thirst between SS and PL (Table 4). Fatigue was lower in SS (vs PL) from 60 to 240 min (p = 0.001 to p = 0.039), while energy was higher in SS (vs PL) over the same time frame (p = 0.007 to p = 0.037). Tiredness was lower (ie, participants felt more awake) in SS (vs PL) at 120 min (p=0.006) and possibly at 180 min (p = 0.092). Concentration was significantly higher in SS (vs PL) at 180 min (p = 0.020) and possibly higher at 60 min (p = 0.055) and 240 min (p = 0.083). No overall (main or interaction) effects were observed in linear-mixed models of other VAS measures, except for a significant increase in thirst regardless of trial (β = 0.006, SE = 0.001, p < 0.001). The AUC was significantly lower in SS for head discomfort (p = 0.012) and fatigue (p = 0.002), whereas AUC was higher in SS for energy (p = 0.010), tiredness (p = 0.026), and concentration (p = 0.026). No AUC differences were found for nausea or thirst (Table 4).

Urine volume was significantly higher in SS vs PL at 60 min post-ingestion (686.2 mL vs 408.9 mL, p < 0.001, respectively). No other timepoints (p = 0.281 to p = 0.839) nor interaction effect with time (p = 0.580) were significantly different between trials, but there was a trend for trial (p = 0.054). Total urine volume over 240 min was significantly higher in SS compared to PL (1248.1 vs 965.1 mL, p < 0.001, respectively) showing that participants urinated more overall within the SS treatment (Table 5). Thus, the AUC was higher in SS for urine volume (p < 0.001) (Table 5). No significant differences were found between trials for weight or USG (Table 6).

Vital Signs

SBP and DBP did not differ significantly between trials overall (main effect of trial, p = 0.442 and p = 0.539, respectively) or across time (interaction term, p = 0.360 and p = 0.334, respectively). However, SBP was significantly higher at 120 min (113.91 ± 12.15 vs 119.00 ± 10.51 mmHg, p = 0.049) and possibly higher at 180 min (119.7 ± 13.3 vs

Table 4 VAS Variables Over Time (Values Were Measured and Reported in Cm) and Area Under the Curve (AUC)

Variable & Time (min)	Placebo (PL)	Safety Shot (SS)	P-value	Cohen's d
Head Discomfort 0†	1.085 (1.341)	0.876 (1.396)	0.326	0.12
Head Discomfort 60†	1.032 (1.111)	0.821 (1.236)	**0.022**	0.17
Head Discomfort 120†	1.242 (1.478)	0.755 (0.787)	0.244	0.31
Head Discomfort 180†	1.297 (1.524)	0.891 (1.099)	0.118	0.31
Head Discomfort 240†	1.968 (2.344)	0.832 (1.191)	**0.003**	0.52
Head Discomfort AUC	305.82 (286.11)	198.27 (196.08)	**0.012**	0.47
Nausea 0‡	0.500 (1.033) 0.100	0.188 (0.318) 0.100	0.154	0.29
Nausea 60‡	0.559 (1.021) 0.200	0.265 (0.400) 0.100	0.176	0.28
Nausea 120‡	0.436 (0.762) 0.150	0.927 (1.997) 0.100	0.873	0.31
Nausea 180‡	0.559 (1.190) 0.100	0.700 (1.265) 0.100	0.904	0.09
Nausea 240‡	0.529 (0.897) 0.100	0.826 (1.646) 0.250	0.802	0.16
Nausea AUC	127.09 (189.79)	146.64 (228.90)	0.648	0.08
Fatigue 0	1.803 (1.517)	1.691 (1.727)	0.712	0.07
Fatigue 60	2.265 (1.721)	1.374 (1.307)	**0.007**	0.51
Fatigue 120	3.124 (1.950)	2.255 (1.857)	**0.028**	0.43
Fatigue 180	2.909 (2.032)	2.253 (1.786)	**0.039**	0.39
Fatigue 240	3.094 (2.084)	2.012 (1.766)	**0.001**	0.62
Fatigue AUC	646.36 (381.99)	465.82 (323.94)	**0.002**	0.59
Energy 0	4.268 (2.368)	4.726 (2.227)	0.157	0.22
Energy 60	4.485 (1.994)	5.203 (2.189)	**0.033**	0.36
Energy 120	4.091 (2.084)	4.758 (2.171)	**0.037**	0.35
Energy 180	4.229 (1.922)	4.853 (2.017)	**0.012**	0.44
Energy 240	4.324 (2.004)	5.165 (2.218)	**0.007**	0.50
Energy AUC	1010.73 (430.51)	1173.73 (462.82)	**0.010**	0.48
Tiredness 0	4.724 (2.500)	4.991 (2.557)	0.485	0.09
Tiredness 60	4.479 (2.231)	4.971 (2.407)	0.190	0.21
Tiredness 120	3.997 (2.191)	5.006 (2.188)	**0.006**	0.48
Tiredness 180	4.135 (1.798)	4.803 (2.320)	*0.092*	0.29
Tiredness 240	4.132 (1.902)	4.929 (2.393)	0.155	0.30
Tiredness AUC	1008.27 (426.56)	1174.18 (435.28)	**0.026**	0.41
Thirst 0	3.894 (2.110)	3.788 (2.328)	0.763	0.04
Thirst 60	4.203 (2.009)	3.856 (2.434)	0.455	0.15
Thirst 120	4.548 (2.121)	4.418 (2.577)	0.808	0.06

(*Continued*)

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Table 4 (Continued).

Variable & Time (min)	Placebo (PL)	Safety Shot (SS)	P-value	Cohen's d
Thirst 180	5.159 (2.154)	4.891 (2.582)	0.525	0.12
Thirst 240	5.306 (2.313)	5.079 (2.845)	0.523	0.10
Thirst AUC	1108.64 (461.53)	1053.27 (559.67)	0.509	0.12
Concentrate 0	5.974 (2.357)	6.168 (2.051)	0.680	0.09
Concentrate 60	4.785 (2.030)	5.347 (1.935)	0.055	0.37
Concentrate 120	5.097 (1.959)	5.470 (1.705)	0.265	0.22
Concentrate 180	5.029 (2.008)	5.668 (1.932)	**0.020**	0.44
Concentrate 240	5.124 (2.122)	5.782 (2.086)	*0.083*	0.33
Concentrate AUC	1219.36 (410.84)	1341.45 (411.25)	**0.026**	0.41

Notes: P-values represent the within-time main effect between the placebo and safety shot trials, adjusted for the effects of age and sex, accounting for repeated measures. P-values in bold are significant (p≤0.05), whereas p-values in italics are trends (p≤0.10). Cohen's d: 0.2=small, 0.5=medium, 0.8=large effect size. † p-values after BoxCox transformation and linear-mixed models on ranked data. ‡ due to non-normality, results presented as mean (SD) median, and pairwise testing using Wilcoxon Signed-Rank test and linear-mixed models on ranked data.

Table 5 Urine Volume (mL) Over Time and Area Under the Curve (AUC)

Time	Placebo (PL)	Safety Shot (SS)	P-value	Cohen's *d*
0min	122.7 (110.5)	134.4 (115.6)	0.555	0.04
60min	408.9 (260.4)	686.2 (312.7)	**<0.001**	1.18
120min	273.9 (138.4)	268.5 (138.9)	0.839	0.04
240min	138.2 (55.5)	164.1 (97.5)	0.281	0.19
Total Volume (cumulative)	965.1 (399.5)	1248.1 (419.8)	**<0.001**	0.92
AUC	62301.80 (24,922.53)	78,438.75 (25,874.17)	**<0.001**	0.86

Notes: P-values represent the within-time main effect between the placebo and safety shot trials, adjusted for the effects of age and sex, accounting for repeated measures. P-values in bold are significant (p≤0.05). Results presented as mean (SD). Cohen's d: 0.2=small, 0.5=medium, 0.8=large effect size.

Table 6 Body Weight, and USG

Variable	Placebo (n=18)	Safety shot (n=17)	p-value
Weight (kg)	82.5 (14.2)	82.48 (14.0)	0.357
USG	1.0161 (0.0073)	1.0152 (0.0082)	0.214

Notes: Results presented as mean (SD), p-values derived from paired t-tests.
Abbreviation: USG, Urine specific gravity.

123.3 ± 9.3 mmHg, p = 0.062), and DBP was higher at 180 min (73.7 ± 10.1 vs 77.2 ± 8.5 mmHg, p = 0.038) in SS vs PL (Table 7). HR may have been higher at 180 min (72.8 ± 10.8 vs 70.2 ± 10.1 mmHg, p = 0.056) in SS vs PL (Table 7).

Adverse Events (AEs)

There were no serious adverse events (AE). However, there were a total of five AEs in this clinical trial. Four AEs occurred during the SS trial where 3 participants felt nauseous (2 were moderate while 1 was mild in nature) that were

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Table 7 Vital Signs Over Time

Variable & Time (min)	Placebo	Safety Shot	P-value
SBP 0	122.0 (10.7)	122.6 (13.1)	0.229
SBP 60	116.8 (13.0)	120.0 (10.4)	0.134
SBP 120	113.9 (12.2)	119.0 (10.5)	**0.049**
SBP 180	116.2 (13.1)	118.9 (11.4)	0.284
SBP 240	119.7 (13.3)	123.3 (9.3)	*0.062*
DBP 0	77.68 (10.3)	78.47 (9.2)	0.589
DBP 60	74.38 (10.9)	77.06 (8.8)	0.110
DBP 120	73.85 (12.0)	75.18 (7.9)	0.422
DBP 180	73.74 (10.1)	77.21 (8.5)	**0.038**
DBP 240	75.41 (10.4)	77.79 (8.8)	0.157
HR 0	69.7 (12.4)	70.0 (11.5)	0.796
HR 60	70.2 (12.7)	70.0 (10.5)	0.846
HR 120	71.6 (10.8)	70.9 (11.4)	0.548
HR 180	70.2 (10.1)	72.8 (10.8)	*0.056*
HR 240	71.0 (10.5)	73.2 (11.7)	0.179

Notes: P-values represent the within-time main effect between placebo and safety shot trials, adjusted for the effects of age and sex, accounting for repeated measures. P-values in bold are significant (p≤0.05), whereas p-values in italics are trends (p≤0.10). Results presented as mean (SD).
Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate. p-values represent paired *t*-test between PL and SS trials.

possibly related to the study product, and one participant developed a rash (mild in nature) that was probably related to the study product. One adverse event occurred during the PL trial, where a participant experienced moderate nausea, possibly related to the assigned study product. Notably, the same participant also reported feeling nauseous during the SS trial. Using a chi-square goodness-of-fit test there were no differences in proportions of AEs among treatments (X^2 = 1.26, p = 0.261).

Discussion

This randomized crossover, placebo-controlled clinical trial sought to determine the impact of a first ever novel blend of dietary ingredients on blood and breath alcohol content, biomarkers of alcohol metabolism and feelings of affect. Based on prior literature,[18] we hypothesized that SS would lower breath and blood ethanol levels by slowing absorption, accelerating alcohol metabolism by increasing acetaldehyde levels, upregulating key regulatory enzymes within alcohol metabolism (ADH, ALDH), and provide a more favorable feeling of cognitive affect compared to PL. Collectively, the results of this study demonstrated these beneficial effects. First, the SS trial had lower breath alcohol levels than PL at each time point (p ≤ 0.05) with medium-to-large effect sizes. Second, serum ethanol levels were significantly lower in the SS trial than PL at 30-, 60-, and 180-min [and trending for change at 45- (p = 0.012) and 90-min (p ≤ 0.10)]. Third, compared to PL, the SS trial had a significantly lower AUC and Cmax for ethanol and significantly higher acetaldehyde and aldehyde dehydrogenase levels. Additionally, there was greater urine output during the SS trial than PL at 60 min, as well as a total cumulative urine output over the 240 min collection period (p ≤ 0.05), suggesting greater clearance of

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alcohol. SS also reported less head discomfort at 60- and 240-min ($p \leq 0.05$), less tiredness at 120 min ($p \leq 0.05$) [and trending for change at 180 min ($p \leq 0.10$)], less fatigue and more energy at 60-, 120-, 180-, and 240-min ($p \leq 0.05$) and better concentration at 180 min ($p \leq 0.05$) [and trending for change at 60- and 240-min ($p \leq 0.10$)] than PL. Overall, there was a more favorable response (as per AUC) for SS vs PL for head discomfort, fatigue, energy, tiredness, and concentration ($p \leq 0.05$). In contrast, there were no differences in nausea and thirst between PL and SS (all $p > 0.10$). Systolic blood pressure was slightly elevated at 120 min ($p \leq 0.05$) [and trending for change at 240 min ($p \leq 0.10$)], diastolic blood pressure was slightly elevated at 180 min ($p \leq 0.05$), and heart rate was possibly elevated (trending) at 180 min ($p \leq 0.10$) in SS vs PL. However, these small transient changes remained well within normal clinical ranges for resting vital signs. Although there were no serious AEs, there were four participants who did encounter AEs during SS that ranged from mild-to-moderate intensity (mostly related to nausea), whereas one participant experienced an AE during PL that was also moderate in nature (ie, nausea); however, there were no differences in the proportions of AEs among treatments. These AEs were not entirely unexpected given that the study design required all participants to arrive in the fasted state to consume straight alcohol (vodka) in the morning hours (0700–1100), which is highly uncommon. Although the precise mechanisms underpinning the efficacy of SS remain unclear, several potential mechanisms are possible. These mechanisms include a faster conversion of ethanol to acetaldehyde, increased activity of aldehyde dehydrogenase (ALDH), inhibition of pro-inflammatory mediators, and enhanced antioxidant activity.

This study reinforces and extends the findings of Lee et al,[18] who reported the beneficial effect of red ginseng on BAC and BrAC. However, whereas Lee and colleagues reported lower BAC and BrAC in only the first hour post alcohol consumption, SS was effective in attenuating spikes in BAC and BrAC over the entire 240-minute post-consumption period versus PL. Similar to the current investigation, Lee and colleagues[18] also reported average differences of 0.01 in BrAC between red ginseng and PL and lower BAC with red ginseng at 30, 45, and 60 min post ingestion. In addition, the same authors observed that red ginseng had a greater plasma acetaldehyde concentration 120 min ($p = 0.020$) after alcohol consumption along with a possibly larger acetaldehyde AUC vs PL ($p = 0.054$).[18] These findings partially agree with our more comprehensive observation of a higher AUC and Cmax for acetaldehyde levels and ALDH activity in the SS trial than PL. Thus, there appears to be an added benefit to the combination of ingredients in SS rather than red ginseng alone in reducing BAC, BrAC, and accelerating alcohol metabolism.

Alcohol consumption can lead to an accumulation of ROS and RNS in the liver[5] which can deplete antioxidants resulting in further oxidative stress[24] and excess ROS that can induce lipid radicles and lipid accumulation in hepatocytes, leading to increased lipid peroxidation.[25] Alcohol consumption can also disrupt intestinal barrier function, allowing bacterial endotoxins such as lipopolysaccharides (LPS) to pass into systemic circulation and induce inflammation.[13] The addition of antioxidants may help lessen oxidative stress caused by alcohol consumption and stimulate ADH and ALDH.[16,19,26] SS includes a collection of ingredients with antioxidant activity such as red ginseng, N-acetyl cysteine [(NAC, which serves as the precursor to glutathione), Dandelion extract,[27,28] *Mucuna pruriens*,[29] Citicoline,[30] and milk thistle (which can increase cellular content of glutathione)[31]]. In fact, cysteine (from NAC) availability in the blood is known to be the rate-limiting substrate for glutathione resynthesis[32] and saponins within ginseng have been shown to increase superoxide radical scavenging activity, inhibit ROS production in the liver,[33,34] and increase hepatic GPX and SOD activity.[35] Additionally, SS contains pectin, an ingredient that has a great affinity for ethanol.[36] Pectin's carboxyl groups tend to interact with ethanol's hydroxyl groups, which could theoretically result in neutralization and detoxification of ethanol (as shown in mice) and its metabolites.[3,36] This interaction with ethanol's hydroxyl groups along with the formation of a pectin complex on the villi of epithelial cells causes the viscosity of intestinal fluids to increase, potentially impeding the absorption of ethanol.[3] Research has shown that dandelion juice can increase plasma concentrations of aldehyde dehydrogenase (ALDH) and enhance the activity of glutathione reductase and catalase (CAT) in erythrocytes. These effects suggest that dandelion juice may effectively reduce oxidative stress in healthy male adults.[37] Theacrine, another prominent ingredient in SS, has also been shown to have antioxidant action and hepato-protective effects.[38] Theacrine has also been shown to boost antioxidant enzymes (SOD, GPX, and CAT), reduce AST and ALT levels, and reduce xanthine oxidase (XOD) and malondialdehyde (MDA), all markers of oxidative stress, on stress-induced liver damage in mice.[38] Thus, we speculate that the combination of these antioxidant and hepato-adaptive ingredients in SS may have helped attenuate the oxidative stress caused by acute alcohol consumption and

upregulate ALDH activity, which subsequently reduced BAC and BrAC. Interestingly, despite the numerically higher ADH activity in the SS trial, we did not observe a significant increase in ADH activity, likely due to low statistical power (ie, 1-β = 23%) and high variability (ie, CV = 18.6%) of this measurement.

Excessive production of ROS and RNS during alcohol consumption overwhelms the body's oxidative metabolic pathways, leading to increased lipid peroxidation of cellular membranes as well as the oxidation of proteins and DNA. These processes contribute to hepatocyte injury and trigger inflammation within the liver.[5] In this regard, several ingredients in SS, such as milk thistle,[39] dandelion extract,[27,40] apple pectin,[41] theacrine,[38] and ginseng,[5] have the potential to reduce inflammation. Antioxidants have been shown to reduce lipid droplets in mice hepatocytes, suppress levels of ROS in mice liver, attenuate the depletion of antioxidant enzymes (ie, GPX, SOD, and CAT), upregulate the rabbit nuclear factor erythroid-2-related factor 2 (Nrf2) signal pathway (to fight against oxidative stress), lower LPS, inhibit the alcohol-induced increase of pro-inflammatory cytokine IL-1β and restore the alcohol-induced decrease of anti-inflammatory cytokine IL-10, and inhibit the Toll-like receptor 4 (TLR4) signal pathway (which contributes to ethanol-induced liver inflammation) in mice.[14] In a previous investigation, researchers tested the effects of the fruit *Hovenia dulcis* (HD) on alcohol-induced hangovers (symptoms at 1-, 4-, and 12 hours post alcohol consumption) and found that HD increased IL-10 levels and IL-10/IL-6 ratio, whereas PL increased IL-6 levels at 4hr and 12hr post alcohol consumption, thus HD helped suppress pro-inflammatory cytokine IL-6 production and manage the inflammatory response to alcohol consumption better than PL.[17] In the same study a positive correlation was found between blood acetaldehyde and inflammatory cytokines (IL-6 and IL-10) and hangover symptom severity.[17] However, it is important to note this is not a universal finding.[11] Furthermore, the application of Ginseng for 30 days suppressed the inflammatory response (serum TNF-α, IL-6, IL-1β, and LPS) by inhibiting the LPS-TLR4-NF-κβ signal pathway in binge-drinking rats.[5] Thus, it is plausible that SS affected the acute hepatocellular inflammatory response elicited by ethanol ingestion. However, given that we did not assess markers of hepatocellular inflammation, this mechanism is speculative and warrants more research. It is also important to note that our study did not examine the long-term (ie, > 4hr) effect or comparative effects of SS vs PL on hangover symptoms (ie, ≥12hr), and thus our results are best viewed within the context of the study design.

During the 4-hour post-consumption period, participants in the SS trial had a significantly greater urine output only at the 60-minute post time point, which contributed to a greater total cumulative urine output (0.28L more than PL on average) over the 240-minute post-consumption period. The increased urine output at 60 min during the SS trial may be due to certain ingredients transiently increasing urine production and/or excretion. For instance, dandelion extract has been posited to be a viable bioactive to treat cystitis (bladder inflammation) by reducing vasopressin and increasing urine production and clearance.[42] Likewise, preclinical data have indicated that milk thistle increases urine excretion in rats without adversely affecting plasma electrolyte levels.[43] Although serum vasopressin or electrolytes were not measured herein, it seems plausible that these bioactives may have led to the transient 60-min post consumption increase in urine output. Hence, more research is required to determine if relevant serum markers (eg, electrolytes and/or vasopressin) are altered following SS consumption.

It is well known that acute alcohol ingestion can lead to dizziness, headache, and fatigue.[3] SS contains several established nootropic ingredients such as caffeine anhydrous,[44] Cognizin® Citicoline,[30,45] Methylliberine (Dynamine®),[46] and Theacrine (TeaCrine®)[47,48] which have been shown to increase energy, focus, and concentration. Citicoline has been shown to increase dopamine levels, while caffeine and Theacrine may increase dopamine transmission, which, in turn, might improve energy and concentration.[30,45,49] Despite Lv and colleagues[19] reporting fewer headaches 24 hours post alcohol ingestion (via hangover survey) with hydrogen water vs a PL, the less head discomfort observed acutely in the current investigation may suggest the possibility of a similar effect with SS. Thus, it is likely that the combination of nootropic/neuroactive ingredients in SS led to the favorable responses we observed for head discomfort, fatigue, energy, tiredness, and concentration. There were a few small, transient increases in SBP/DBP and HR after SS consumption, which may be attributed to the caffeine content;[50] however, on average, all of these small elevations were well within normal clinical limits.

Despite our best efforts, this study has inherent limitations that should be acknowledged to provide further insight and guide future research. We acknowledge that there are polymorphisms of the enzymes that regulate alcohol metabolism,

which may have impacted the findings in this acute study,[6,17,26,51,52] however we attempted to control this potential confounder by using a crossover design where each person served as their own control. This type of design enhances data sensitivity as the inter-individual variability is minimized. The results of this investigation also need to be placed in context for current and future research as comparisons need to take into consideration the volume and type of alcohol ingested. To further expand the implications of this intervention, future studies may contemplate using more sensitive techniques of liver function (eg, isotropic tracers, metabolic imaging), directly measure potential mechanisms of action (eg, hormones that influence fluid balance, anti-inflammatory/antioxidant status, and metabolic rate) and evaluate physical coordination, executive function, and if there are any next-day effects of use (ie, 12hr and/or 24hr post) of SS when ingesting alcohol. More research is also needed to better understand how SS influences pharmacokinetic modeling (ie, absorption, reduction and clearance, and excretion) of alcohol in the blood and breath after ingestion.

Conclusion

This investigation uniquely examined not just a single ingredient but a novel blend of dietary ingredients on acute blood and breath alcohol levels along with biomarkers of alcohol metabolism and key regulatory enzymes within alcohol metabolism. This investigation demonstrates the acute benefits of SS on blood and breath alcohol levels, biomarkers of alcohol metabolism, key enzymes within alcohol metabolism, urine output, and feelings of affect over a 4-hour post-alcohol consumption period. In line with our hypothesis, SS was effective in reducing elevations in blood and breath alcohol concentrations, as noted by the reductions in BrAC and BAC, and the elevations in acetaldehyde and ALDH levels. SS also had a more favorable response as compared to PL for head discomfort, fatigue, energy, tiredness, and concentration, while there were no reported differences in nausea and thirst. Future research needs to identify direct mechanisms of action, directly measure anti-inflammatory/antioxidant status, evaluate physical coordination, executive function, and hangover severity/symptoms. Nevertheless, these results indicate that SS can more optimally manage the deleterious effects of alcohol and may offer some relief to those individuals suffering from the acute effects of alcohol.

Data Sharing Statement

The data from this study are owned by the sponsor and may contain confidential information. However, individual deidentified participant data and relevant study documents may be made available upon reasonable request. Specific details regarding the data and documents that can be shared, as well as the procedures for accessing them, can be provided upon inquiry. Data access will be granted based on the request's merit, subject to appropriate confidentiality agreements, and will be available for a defined period to ensure compliance with regulatory and ethical guidelines. Inquiries should be directed to the corresponding author Michael B. La Monica.

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Disclosure

This study was conducted at The Center for Applied Health Sciences in Ohio, where Tim N. Ziegenfuss, PhD, is a principal owner. While Tim Ziegenfuss PhD had no direct involvement in the execution of this study (conducted and led by the PI, Michael La Monica, PhD), the data collection or statistical analyses of this study, he does have several granted patents on theacrine and methylliberine. He is disclosing his intellectual property interests to maintain research integrity and transparency. The authors declare no other conflicts of interest.

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