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EFFECT OF A NOVEL DIETARY SUPPLEMENT, FSD-F2R6, ON ALCOHOL METABOLISM, MENTAL CLARITY, AND HANGOVER SYMPTOMS AFTER ALCOHOL CONSUMPTION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY

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ABSTRACT

A novel dietary supplement was developed to help accelerate alcohol metabolism, enhance cognition, reduce hangover symptoms, and provide nutritional support in intoxicated individuals. Here, we report the results from a clinical trial using FSD-F2R6 on blood alcohol concentration (BAC) and measures of impairment in healthy participants in a state of acute alcohol intoxication. A randomized double-blind placebo-controlled crossover clinical trial was conducted with healthy participants (n=26). Each participant consumed a calibrated amount of alcohol (1 g/kg) in each session, achieving a peak BAC in the range of 0.07-0.11%. Participants consumed either a single dose of FSD-F2R6 or placebo. BAC and various visual analog scales, hemodynamic parameters, cognitive tests, and hangover assessments were conducted post-treatment. Compared with placebo, FSD-F2R6 significantly reduced BAC levels post-treatment. Additionally, 70.8% (17/24) of rapidly responding participants had an average 40% greater BAC decrease with FSD-F2R6 at 30 min than with placebo. FSD-F2R6 also attenuated alcohol-induced increases in heart rate and decreases in blood pressure. Treatment with FSD-F2R6 significantly improved cognition, mental clarity, energy, alertness and clear-headedness, and the symptoms of alcohol intoxication, as early as 30 min post-treatment. FSD-F2R6 significantly reduced hangover symptoms, with a three-fold reduction in headache at 4 hours and a four-fold reduction in headache at 8 hours. There were no serious adverse events. FSD-F2R6 is a safe and effective dietary supplement to mitigate the immediate effects of excess alcohol consumption efficiently by reducing BAC, improving cognition, reducing the signs and symptoms of alcohol intoxication, and reducing hangover effects.

KEYWORDS: acute alcohol intoxication, dietary supplement, ethanol metabolism, cognition, mental alertness, dihydromyricetin.

INTRODUCTION

There are few options for the treatment of excess alcohol consumption and reversal of acute alcohol intoxication. In general, hydration, multi-vitamins or other household remedies are employed, but these do not address the acute effects of alcohol. While there are few products available to help reduce alcohol-induced hangovers, there are few options that help with immediate effects of excess alcohol intoxication, including in a hospital setting except providing nutritional support and let the natural metabolism of the body eliminate alcohol from the body. A scientifically sound dietary supplement with fortified nutrients can play a major role in addressing the immediate effects of alcohol on human body and help recover faster.

Thus, a dietary supplement addressing the immediate effects of excess alcohol consumption would be of great value, allowing the affected individuals to return to their normal state more quickly. Such a product could also be helpful when one is in a vulnerable state due to excess alcohol consumption, helping the individual to return to a normal functioning and normal cognitive state. An approach to address excess alcohol in the body is to

prevent and/or reverse the physical and mental insult caused by excess alcohol intake and facilitate faster elimination (or metabolism) of ethanol. The liver metabolises most of the alcohol through the alcohol dehydrogenase (ADH)-aldehyde dehydrogenase (ALDH) system.[1] Additionally, the microsomal ethanol oxidizing system (MEOS) and catalase also metabolize ethanol in its conversion from ethanol to acetaldehyde.[1] All enzymes that oxidize ethanol to acetaldehyde require NAD^+ as a cofactor, which is reduced to NADH.

A target profile was established for a potential product with the following functions to treat and reverse acute alcohol intoxication: (1) improvement of mental alertness and cognitive functions in less than 30 min, (2) acceleration of alcohol metabolism, (3) reduction of hangover symptoms, and (4) general nutritional support. A comprehensive review of the literature revealed several natural products, vitamins and other food/dietary supplements that can potentially achieve these functions, and a product formulation was developed consisting of food and dietary supplement ingredients. It must be noted that the product is intended to be used as an aid for rapid recovery from acute alcohol intoxication and is not intended as a therapeutic for chronic alcohol consumption. The formulation is classified as a dietary supplement in the USA. Various functional ingredients in this formulation, FSD-F2R6, include dihydromyricetin, fructose, methylliberine, caffeine, huperzine A, isoquercitrin, milk thistle, various B vitamins, and L-phenylalanine.

Here, we report the results of a double-blind, randomized, placebo-controlled crossover clinical trial investigating the safety and efficacy of the dietary supplement FSD-F2R6 in acute alcohol intoxication.

MATERIALS AND METHODS

Ethical Considerations

The clinical study protocol and all associated forms including informed consent forms were reviewed and approved by an external institutional review board commissioned by Advarra (IRB, ID: Pro00079581). The approved clinical study protocol was submitted to the clinical trial registry at ClinicalTrials.gov (ID: NCT06505239) and was approved prior to the screening of any potential participants. The study was conducted and the data was collected at the Applied Science Performance Institute (Tampa, Florida).

Test clinical materials (FSD-F2R6 and placebo)

The investigational product, FSD-F2R6, is a powder which was dissolved in 475mL (16oz) of water prior to consumption. It contains a proprietary blend of dihydromyricetin (from vine tea extract), L-phenylalanine, green tea extract (caffeine), isoquercitrin, methylliberine, milk thistle extract, and *Huperzia serrata* extract.[2] among other ingredients, and conforms to the dietary supplement regulations of the US FDA. In addition, this formulation includes a blend of vitamins, thiamine hydrochloride (vitamin B1, 1.4 mg), riboflavin (vitamin B2, 5 mg), niacin (as niacinamide, 10 mg), pyridoxine hydrochloride (vitamin B6, 10 mg), and methylcobalamin (vitamin B_{12}, 178 µg). For flavor, taste and other functional reasons, sodium citrate, magnesium citrate, citric acid, monopotassium phosphate, xanthan gum, sucralose and natural flavors in various quantities are included in the formulation. The placebo was a powder blend containing citric acid, xanthan gum, sucralose, colors and natural flavors. The placebo was designed to mimic the color, flavor and taste of the active dietary supplement, FSD-F2R6.

The placebo and FSD-F2R6 were filled in identical aluminum sachet packets for the purpose of blinding and were labeled A (stands for active) and B (stands for placebo). These labels were blinded to the clinical investigation team, as well as to the participants. The clinical trial materials, including placebo, were manufactured and packaged in the United States of America under NSF-GMP (food and dietary supplement regulations) conditions. FSD-F2R6 and matching placebo were stored at 2-8 °C until use.

A single dose of FSD-F2R6 or placebo (a single sachet) was administered orally after participants had consumed a prescribed quantity of alcohol (*vide infra*), to achieve a consistent target alcohol concentration in each participant, as measured by a breathalyzer.

Study Participants

Healthy male and female participants from the Tampa Bay area were recruited through word of mouth, email outreach and digital platforms. Each subject participated in the study for approximately two weeks.

Study Protocol

The investigation was designed as a double-blind, randomized, placebo-controlled crossover trial to assess the effects of FSD-F2R6 versus a placebo in alcohol-intoxicated healthy volunteers. During this crossover trial, each participant attended two sessions. In the first session, each participant was randomly assigned to receive either FSD-F2R6 or placebo as the first study treatment, in an intoxicated state. In the second session, each participant received the alternate study treatment from that in the first session, again in an intoxicated state. The impact of the study treatments on alcohol concentrations in the body, cognition, motor skills and any treatment-related adverse effects in participants under alcohol intoxication were investigated. Both the participants and the investigators remained unaware of the intervention assignments. The randomization table and associated lists were maintained separately by a table manager. The sample size necessary to achieve 80% statistical power at a 5% significance level was determined to be 24 participants completing both sessions.

The primary objective (primary outcome) of this study was to assess the safety, tolerability and efficacy of FSD-F2R6 in accelerating blood alcohol concentration (BAC) and alleviating symptoms of alcohol intoxication compared with placebo. Additional assessments included blood pressure (BP), heart rate (HR), respiratory rate (RR), oxygen saturation, and body temperature. Multiple visual analog scales (VAS) and questionnaires, as well as psychomotor and cognitive tests, were employed to investigate motor and cognitive functions. Alcohol hangover scales were used to test for symptoms associated with hangover, including headache.

Compliance with the trial was based on subject self-reporting of inclusion/exclusion criteria, followed by on-site testing of vital signs, breath alcohol, urine drug testing, and urine pregnancy testing (females). Study treatments were directly measured, and their administration was monitored by the research staff to ensure full compliance.

Eligibility Assessment

Candidates for the clinical study were screened for eligibility within a 28-day window prior to treatment and prior to enrollment in the study. Candidates (n=385) who agreed and provided informed consent (ICF), as well as demographic and medical information, were evaluated for eligibility based on inclusion and exclusion criteria (Table 1). Following enrollment, on the day prior to the study visit, blood samples were taken for baseline assessment.

Table 1: Inclusion and exclusion criteria.

Inclusion Criteria
● English-literate, non-smoking (> 6 months) ● Men and women aged 18 to 45 years ● Body mass index (BMI) of 18.5 to 32.0 kg/m2, and weighing between 110 and 220 lbs (50-100 kg) ● Free of the diseases listed in exclusion criteria according to their medical history ● An ECG value of ≤ 440 msec for males and ≤ 460 msec for females, as measured by an FDA-cleared ECG device (6-lead device, KardiaMobile), administered by the investigator ● Capable of consuming 4-6 standard drinks for women or 5-7 standard drinks for men on a single occasion without experiencing moderate sedation, vomiting, or aggression, to be eligible for the study. Moderate sedation is defined as the subject must be able to communicate and follow simple directions following the consumption of indicated number of drinks ● Agree not to get tattoos or body piercings, or receive vaccines during the study period, or 7 days prior to the study period ● Female subjects who must test negative on a urine pregnancy test, and cannot be pregnant or lactating. All subjects are required to either refrain from sex or use at least one form of contraception throughout the study, including a condom or either an oral or intrauterine contraceptive ● Men who must agree not to donate sperm for 90 days following the trial ● Experienced at least 2 hangovers ● Clinical laboratory values within the most recent acceptable laboratory test range, and/or values are deemed by the Investigator /Sub-Investigator as "Not Clinically Significant" as per CBC/CMP, urinalysis, and coagulation testing
Exclusion Criteria
● A known history or presence of any clinically relevant conditions affecting the liver, kidneys, gastrointestinal system, cardiovascular system, cerebrovascular system, lungs, endocrine system, immune system, musculoskeletal system, nervous system, psychiatric state, respiratory system, skin, or blood, unless deemed not clinically significant by the Investigator/Sub-Investigator. This includes a significant history or current issues with gastrointestinal pathology, such as chronic diarrhea or inflammatory bowel diseases, or conditions affecting drug absorption, distribution, metabolism, or excretion ● Major surgery within the past 6 months, a history of seizures, significant head trauma, or neurosurgery, or any clinically significant illness within 30 days prior to dosing are also excluded ● Are on a ketogenic or very low carbohydrate diet within the past 30 days. ● Significant physical or organ abnormalities, a positive screening for a HIV, Hepatitis B or C (as determined by medical health questionnaires), or positive test result for drugs with abuse potential (cannabis, amphetamines, barbiturates, cocaine, opiates, phencyclidine and benzodiazepines) ● Alcohol-naïve ● Positive pregnancy test

- A history of significant alcohol sensitivity
- A history of adverse reactions to power (energy) drinks or caffeine,
- Severe food allergies, or dietary restrictions.
- Allergic reactions to any ingredients in the FSD-F2R6-A-CP and placebo.
- A psychiatric history of certain disorders, a first-degree relative with specific psychiatric or alcohol use disorders,
- An intolerance to blood sampling, recent blood or plasma donations within the past 60 days.
- Recently used enzyme-modifying drugs within the previous 30 days including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John's Wort, and rifampicin).
- Current or past history within the last 2 years of alcohol or drug dependence (excluding caffeine and nicotine).
- Current or past history within the last 5 years of major depressive disorder, obsessive-compulsive disorder, panic disorder, anorexia nervosa, or bulimia nervosa. First-degree relative with current or historical Alcohol Use Disorder (AUD).
- Intolerance to and/or difficulty with blood sampling through venipuncture or indwelling catheter.
- Used of prescription medication (other than contraception or occasional paracetamol) or over-the-counter medications including supplements within 14 days prior to session 1,
- A positive alcohol test at check-in on treatment day,
- Recent tattoos or piercings (within 7 days of study enrollment)
- Any condition deemed by the Investigator or Sponsor to interfere with study participation was excluded.

Treatment Session 1 (Day 1)

A schedule of events for participants during a treatment session is shown in Figure 1 and a list of assessments at various time points is shown in Table 2. All participants fasted for at least 10 h prior to their arrival on the treatment day. First, various assessments were taken, including vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, body temperature), height, weight, point of care (POC) urinalysis to confirm eligibility status, breathalyzer confirmation of zero alcohol status, and point of care urine drug screening to ensure no intoxicating narcotics. Females underwent pregnancy testing through urinalysis and medical health questionnaires.

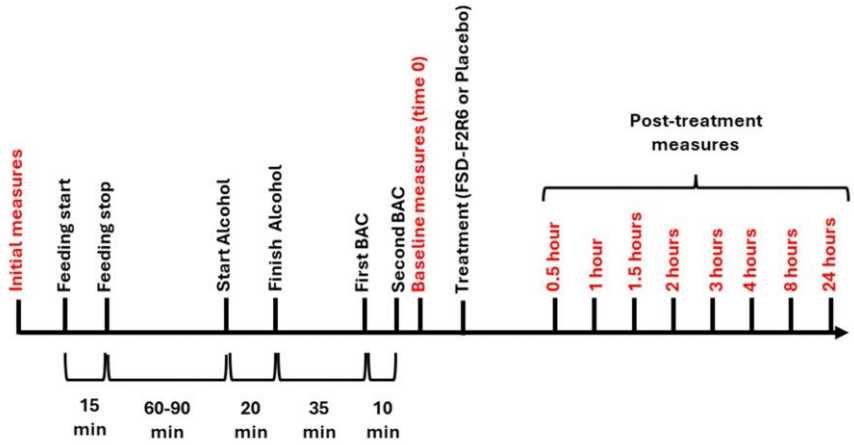

Figure 1 Timeline of events for participants during each treatment session. The timeline shows when participants received a meal, consumed alcohol, had BAC measurements by breathalyzer, and consumed treatment (FSD-F2R6 or placebo). This timeline is representative of a participant whose BAC stabilized and was not rising after the second BAC measurement. For participants whose BAC had not stabilized within 0.01% units, additional BAC measurements were obtained until stable and before treatment was given. Events in red indicate the collection of outcome measures and are described in a separate table of outcome measures (Table 2). Initial measures were taken approximately 1.5 h prior to treatment with either FSD-F2R6 or placebo. Participants underwent a total of two of these treatment sessions in this crossover study.

Table 2 Outcome measurement schedule.

Outcome Measure	-90 min	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	8 h	24 h
Urine Drug Test	X									
Urinalysis	X									X
Pregnancy Test	X									
CBC, CMP, Coagulation	X									X
BAC	X	X	X	X	X	X	X	X		
Vital Signs (BP, HR, RR, O_2SAT, BT)	X	X	X	X		X		X		
Intoxication VAS	X	X	X	X		X		X		
Bond & Lader VAS	X	X	X	X		X		X		
Headache Severity VAS	X	X	X	X		X		X	X	
AHSS VAS									X	X
SIHSS									X	X
DRUID	X	X	X	X		X		X		
Trail-making Test	X	X	X	X		X		X		
DSST	X	X	X	X		X		X		

Notes: *Readings at 0 h are baseline, pre-treatment observations. BAC was performed first when multiple tests need to be conducted at a time point. Vital signs were assessed after BAC. Intoxication VAS, Bond & Lader VAS and Headache Severity VAS were performed after vital signs, where applicable.*

Abbreviations: *AHSS, acute hangover severity score; BAC, blood alcohol concentration; BP, blood pressure; BT, body temperature; CBC, complete blood count; CMP, comprehensive metabolic panel; DSST, digit symbol substitution task; h, hour; HR, heart rate; min, minutes; O_2SAT, oxygen saturation; RR, respiratory rate; SIHSS, single item hangover severity score; VAS, visual analog scale.*

Participants then underwent a standardized feeding (food bar, 300 calories) and were instructed to finish the entire feeding within 15 min. No additional food was ingested until given a second feeding ~3 h post-treatment administration (calculated from the time of treatment ingestion). Water (250 mL) was allowed, if thirsty, and/or a medical need. All water consumption was recorded.

Approximately 60-90 min post-feeding, alcohol was administered to achieve a target stable breath alcohol concentration (%BAC) of at least 0.07% (note: The readings from the breathalyzer were recorded as BrACs, which were then automatically converted to BAC (g/dL) by the apparatus and entered into the database as described below). Participants received a volume of vodka (~38-40% v/v) equivalent to 1.0 g of alcohol per kg of bodyweight (1 g/kg) in order to achieve the targeted BAC between 0.07% and 0.11%, as outlined by Ferreira et al.[3] Participants were instructed to consume the alcohol within 20 min. Following the alcohol consumption, breathalyzer readings using the AlcoMate AccuCell Model AL9000 (AK GlobalTech, Palisades Park, NJ, USA) were conducted at 35 and 45 min to determine BAC. The goal of this protocol with multiple BAC checks was to ensure that the ingested alcohol had been absorbed and that a peak BAC was achieved prior to administration of the treatment. Participants with a BAC of 0.07 or higher, demonstrating stability (i.e. ≤ 0.01 variation between two consecutive BAC readings) were administered the treatment. If BAC readings exceeded 0.07% and continued rising by ≥0.01, breathalyzer tests were repeated every 10 min until stable with a difference < 0.01. If BAC failed to stabilize and dropped below 0.07%, an additional alcohol dose (20% of the previous amount) was given, followed by a 25-minute waiting period (5 min for consumption, 20 min for absorption). BAC was then reassessed every 10 min until stabilization at or above 0.07% until a stable BAC was observed. Each subject was then given a single dose of treatment (either FSD-F2R6 or placebo), to be consumed within 5 min.

Subsequently, breathalyzer alcohol tests, cognitive, motor, safety and hangover assessments were performed at scheduled time points for up to 4 h post-treatment administration in all participants and 8 h post-treatment in a subset of participants. Participants underwent an additional breathalyzer test before discharge to ensure that their BAC was no more than 0.03%. In addition, for the safety and security of participants, the site investigator was ultimately responsible for determining whether a participant was ready for discharge. All participants were transported from the clinical site to their respective destinations using a cab service paid for by the clinical site.

24 h Follow-up Tests for Treatment Session 1 (Day 2)
Blood was collected for complete blood count (CBC), comprehensive metabolic panel (CMP) and coagulation testing 18-24 h after the ingestion of the treatment. Participants then underwent a point-of-care urinalysis and completed a single item hangover scale (SIHSS) test, alcohol hangover severity scale (AHSS) test, and reported any adverse events.

Treatment Session 2 (Day 3)
After the 3-day minimum washout period, each participant reported back to the laboratory for the cross-over investigation where the Day 1 testing was repeated

and the second treatment was administered (either FSD-F2R6 or placebo). All procedures were identical except the treatment choice.

24 h Follow-up Tests for Treatment Session 2 (Day 4)
Participants repeated the steps of the 18-24 h follow-up following the second treatment. This completed the participation of each participant in the study.

Adverse Events
Participants were monitored for adverse events during visits and instructed to report any issues, concerns or adverse events via email post-study.

Assessments for Study Outcomes
Outcome assessments were conducted during each on-site visit by the participants according to the schedule shown in Table 2. Overall, all assessments were performed without any challenges and were recorded. The data were stored on in-house data servers at ASPI, and the database was locked after the completion of data collection from all participants. All assessments conducted during this clinical trial are shown in Table 2 and were recorded at the designated times.

Vital Signs
Blood pressure (using a Bioland Model 2005-1 monitor, Bioland Technology, Shenzhen, China), oxygen saturation and heart rate (using an Einstein Associates Model 500BL, Einstein Associates, New York, NY, USA), body temperature (using a Chunni Model CN520, Chunni Medical, Guangzhou, China), and respiratory rate (manual count for 15 seconds × 4) were recorded.

Blood Alcohol Concentration (BAC) and Breath Alcohol Concentration (BrAC) Measurement
BrAC was measured for each subject using the AlcoMate AccuCell Model AL9000 (AK GlobalTech, Palisades Park, NJ, USA) following manufacturer instructions to verify sobriety at baseline (prior to consumption of alcohol at time 0 min) and track alcohol concentrations post-treatment. The readings from the breathalyzer were recorded as BrACs, which were then automatically converted to BAC (g/dL) by the apparatus and entered into the database. It is well-established that there is a strong concurrence between ethanol concentration in the blood and in the lungs, allowing reliable estimation of systemic alcohol levels through BrAC.[4] Data and results are reported as %BAC (e.g., 0.08% BAC = 0.08 g/dL or 80 mg/dL) for further discussions and analysis in the current study.[5] Those participants with a greater decline in %BAC after consuming FSD-F2R6 than that after placebo in the first 30 minutes are defined as "rapid responders" in this study.

Urinalysis
A 14-parameter urinalysis was conducted using the Life2O version 2.0 kit (Life2O, Boston, MA, USA) following manufacturer guidelines, measuring urobilinogen, bilirubin, ketones, creatinine, blood, protein, microalbumin, nitrate, leukocytes, glucose, specific gravity, pH, ascorbate, and calcium.

Complete Blood Count (CBC)/Comprehensive Metabolic Profile (CMP)/Coagulation Testing
Blood samples were collected at designated time points before and after the study. Samples were analyzed for CBC, CMP, and blood coagulation (fibrinogen) at Labcorp, Burlington, NC, USA.

Pregnancy Testing
Female participants were screened at baseline and prior to each visit using the MomMed® HCG25 urine test (MomMed, Newark, DE, USA).

Intoxication Visual Analog Scale (VAS)
Subjective intoxication, as measured by cognitive impairment, mental fatigue, and headache severity, was assessed using a 0–100 mm VAS as previously described.[6] Headache severity was assessed for 4 h in all participants (n=24), with a subset of participants reassessed at 8 h (n=13).

Bond-Lader VAS
The Bond and Lader is a self-reporting tool used to subjectively assess the state of a participant's mood.[7] Thus, alcohol-induced mood and cognitive changes were recorded using bipolar adjective pairs, including (i) Clearheaded–Muzzy, (ii) Clumsy–Well-Coordinated, (iii) Energetic–Lethargic, (iv) Drowsy–Alert, and (v) Mentally Slow–Quick-Witted.

Acute Hangover Severity Scale (AHSS)
The AHSS assesses hangover symptoms where 12 items describing the severity of hangover can be rated from 0 (absent) to 10 (extreme). The ratings of all items were averaged to obtain the AHSS score which was used for further analysis.[8]

Single Item Hangover Severity Scale (SIHSS)
The SIHSS is a single-item questionnaire examining daily functioning of the participants. Overall SIHSS severity was measured on a numerical scale from 0 characterizing 'no hangover symptoms', to 10 characterizing 'very severe hangover symptoms'.[9]

DRUID® App (software tool)
This was an experimental assessment, to understand the effectiveness and relevance of this software tool on cognition and motor assessment. Cognitive and motor impairment was evaluated using the DRUID® app (Impairment Science, Boston, MA, USA) , which assesses reaction time, balance, and decision-making.[10] It is a 3-minute test and was used to generate a single impairment score (25–75), with higher scores indicating greater impairment.

Digit-Symbol Substitution Task (DSST)
The DSST examines cognitive function via a 3-minute task requiring digit-symbol matching (Inquisit Web

version 6.6, Millisecond Software, LLC, Seattle, WA, USA).[6] The overall outcome metrics are: (1) number of correct responses (correct response), with a higher count indicating better accuracy, (2) error count, with lower responses being desirable for reduced errors, and (3) DSST response time (in seconds per correct responses), with a lower value being desirable, and indicating a faster processing speed.

Trail Making Test (TMT)

The TMT evaluated cognitive functions such as attention, processing speed and executive function, and has been used to assess cognitive functions.[11] This assessment consisted of 2 tasks, the first (Trail 1) of which contains exclusively numeric digits where participants link a series of ordered numbers in the fastest time possible. The second (Trail 2) involved more nodes with both numbers and letters collectively, also to be completed in the fastest time possible. Shorter times (i.e. faster task completion) suggest less severe intoxication than longer task-completion times. This assessment was performed using Inquisit Web version 6.6 by Millisecond Software, LLC (https://www.millisecond.com/).

The maximum intoxication point (designated as time 0 h), when the BAC was at its peak after the consumption of alcohol in each subject, was considered baseline for comparisons and the treatment was administered at this time. The measurements at -90 mins were first recorded in a fasted state, prior to alcohol ingestion.

Statistical Analysis

Statistical analyses were conducted using JASP version 0.19.3, Microsoft Excel, and GraphPad Prism Version 10. Data are reported as mean ± standard deviation in the tables, and standard error of the mean in the figures. Effect size was calculated using Cohen's *d* and described as trivial (0-0.19), small (0.2-0.49), moderate (0.5-0.79) and large (0.8+). Normality and variance assumptions were tested using Shapiro-Wilk test for normality. Due to deviations from normality, data were transformed using Rankit's rank-based normal scores before inferential analyses.[12] Generalized mixed-effects models were used to examine time and treatment effects, except for blood markers, which were analyzed solely by time. Pairwise comparisons were performed using sequential *t*-tests with Bonferroni correction. For the Bond-Lader VAS (Drowsy-Alert) analysis, when the baseline values between the two treatment groups differed significantly, all data points were centered by subtracting each treatment's baseline mean, ensuring an equalized baseline. Area under the curve (AUC) was calculated using the trapezoidal method, with Wilcoxon's signed-rank test for significance and rank-biserial correlations (rrb) for effect size estimation. Statistical significance was set at $p < 0.05$ for all analyses and indicated by a "*", unless stated otherwise.

RESULTS

We hypothesized that FSD-F2R6 would promote alcohol metabolism and lower blood alcohol levels faster than a placebo. We also hypothesized that FSD-F2R6 would stabilize hemodynamic changes, improve cognitive function, and improve hangover symptoms in the setting of acute alcohol intoxication, compared to placebo.

A total of 385 participants were screened, and 26 participants were enrolled after completing screening and providing informed consent. Of these 26 participants, two participants (one male and one female) completed one session but did not complete the second session. Thus, 24 participants completed both study treatments in the crossover study. The CONSORT flow diagram is shown in Figure 2.[13] The study enrolled participants from July 2024 to November 2024 and concluded after enrollment was complete.

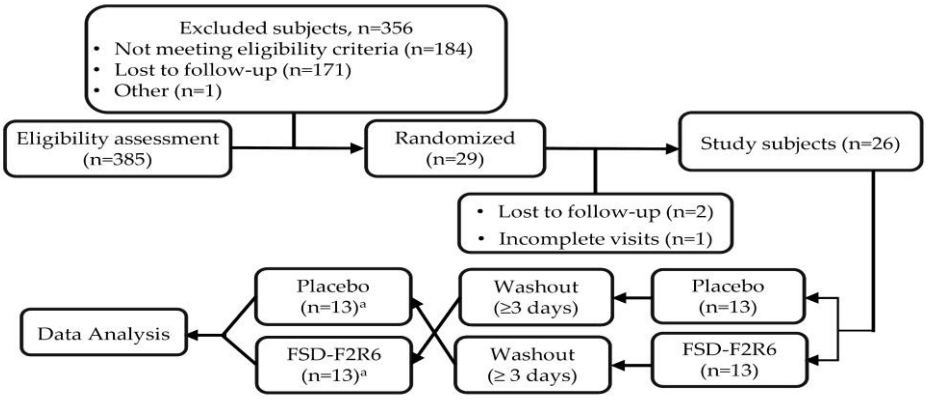

Figure 2 CONSORT diagram for participants in the trial. Number of participants at each step are indicated. Note: [a]Thirteen participants started each of the second treatment sessions, but only twelve finished the second session in both the FSD-F2R6 and placebo groups.

Table 3 presents the demographics and characteristics of the 26 participants who were enrolled in the trial. Among all study participants, 27% (n=7) were male and 73% (n=19) were female participants. The average weight of

the participants was 75.3 ± 12.8 kg, and the average age was 32.8 ± 7.1 years. Study participants included Caucasian/white (n=14), African American/Black (n=3), Asian (n=3) and Hispanic (n=6) ethnicities. At the outset, all participants were able to consume the treatments without any issues concerning palatability.

Table 3: Demographic data of the study participants.

Total Study Participants (n)	26
Male (n)	7
Female (n)	19
Weight (kg)	75.3 ± 12.8
BMI (kg/m^2)	26.0 ± 3.1
Age (years)	32.8 ±7.1
White/Caucasian	14
Black/African American	3
Asian	3
Hispanic or Latino	6

Notes: *Weight, BMI and age are reported as mean ± standard deviation.*

Abbreviations: *BMI, body mass index.*

Blood Alcohol Concentration (BAC)

BAC measurements over time for the placebo and FSD-F2R6 groups are shown in Table 4. Alcohol ingestion elevated BAC levels from 0.00% at -90 min to above 0.10% at 0 min. Prior to administration of either placebo or FSD-F2R6, (time 0), there was no significant difference in BAC between the two groups (0.1065 ± 0.0134% in the placebo and 0.1073 ± 0.0152% in the FSD-F2R6 group, p=0.726). For every time interval, FSD-F2R6 resulted in lower BAC compared to placebo. Comparison of the two treatment groups revealed that FSD-F2R6 significantly reduced BAC compared with placebo at 30, 60, and 240 min. There was also a statistical trend for FSD-F2R6 to reduce BAC at 90 and 180 min. Finally, treatment with FSD-F2R6 led to a significant reduction in blood alcohol AUC over the 4 h time course (Table 4). Differences in BAC and AUC with FSD-F2R6 all had a moderate effect size with Cohen's $d \geq 0.40$.

Table 4: Time course of BAC measurements and AUC.

Time (min)	FSD-F2R6 Mean (SD)	Placebo Mean (SD)	Difference (FSD-F2R6 – Placebo)	*p*-value	*d*
0 (BAC)	0.1073 (0.0152)	0.1065 (0.0134)	0.0007	0.726	0.072
30 (BAC)	0.0824 (0.0152)	0.0851 (0.0137)	-0.0027	0.033*	-0.452
60 (BAC)	0.0737 (0.0146)	0.0770 (0.0122)	-0.0034	0.021*	-0.523
90 (BAC)	0.0676 (0.0134)	0.0701 (0.0136)	-0.0025	0.079[a]	-0.400
120 (BAC)	0.0615 (0.0143)	0.0631 (0.0143)	-0.0016	0.191	-0.285
180 (BAC)	0.0495 (0.0148)	0.0522 (0.0142)	-0.0028	0.066[a]	-0.407
240 (BAC)	0.0329 (0.0143)	0.0355 (0.0140)	-0.0026	0.041*	-0.463
AUC	15.0408 (3.3347)	15.6132 (3.0886)	-0.5724	0.026*	-0.487

Notes: *Values are reported as mean (standard deviation) for all participants (n=26). For BAC measurements, p-values are derived the from comparisons of estimated marginal means in linear mixed effect models, adjusted for sex, age, and weight. For AUC, the p-values are derived from a paired samples t-test comparing the mean AUCs. *, p < 0.05 between the groups within the time-point; [a], statistical trend between the groups within the time point, p = 0.5-0.10; d = Cohen's d between group effect size.*

Abbreviations: *AUC, area under the curve; BAC, blood alcohol concentration.*

In a separate analysis, the acute effects of treatment with FSD-F2R6 were compared with placebo at the 30 min time point. Participants who had a greater percent reduction in BAC with FSD-F2R6 compared with placebo at this timepoint were deemed rapid responders to FSD-F2R6 treatment. Among the rapid responders (70.8%), the response rates in males and females were 83.3% and 66.7%, respectively (Figure 3A). Figure 3B shows percent BAC reduction from all, male and female rapid responders. Based on the BAC reductions in Figure 3B, a percent enhancement in alcohol metabolism was calculated. As shown in Figure 3C, the percent enhancement was calculated to be 40.7% in all rapid responders, 46.6% in male rapid responders, and 38.3% in female rapid responders. Thus, in the first 30 min, BAC levels decreased 40.7% faster in rapid respondents after consuming FSD-F2R6 as compared with placebo. Overall, response rate and percent enhancement at 30 min were similar between male and female rapid responders.

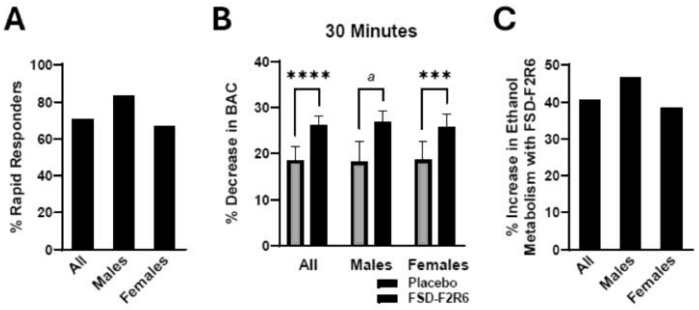

Figure 3 Rapid responders and reduction in blood alcohol concentration (BAC) in participants completing both sessions (n=24). Rapid responders (n=17) are defined as participants who had a greater percent BAC reduction with FSD-F2R6 compared with placebo at 30 min post-treatment. (A) Percent of rapid responders among all, male and female participants. (B) Percent decrease in BAC from baseline at 30 min with both FSD-F2R6 and placebo treatment in all (n=17), male (n=5), and female (n=12) rapid responders. (C) Percent increase in alcohol metabolism with FSD-F2R6 relative to placebo in all, male, and female rapid responders at 30 min. Note: ****, $p < 0.0001$; ***, $p < 0.001$; [a], $p = 0.0625$ by paired Wilcoxon test.

Physiological Outcomes

Heart Rate

Intoxication (prior to treatment) resulted in heart rate increases with placebo showing an increase from -90 min (71.2 ± 14.3 bpm) to 0 min (80.6 ± 11.7 bpm) and FSD-F2R6 also increasing from -90 min (69.4 ± 11.8 bpm) to 0 min (79.3 ± 12.1 bpm) (Figure 4A). Results relative to baseline values demonstrated a significant group effect (p=0.04) and time effect (p < 0.01), but no significant interaction (p=0.338). Pairwise differences within groups for placebo, demonstrated that values tended to decrease from 0 to 120 min but rebounded at 240 min. FSD-F2R6 demonstrated significantly lower heart rates at 30, 60, and 120 min compared to baseline (p=0.04, 0.01, and 0.03, respectively). Pairwise differences between groups revealed that the placebo group had a higher heart rate than FSD-F2R6 overall and specifically at 30 min (p=0.01, d= -0.36), 60 min (p=0.03, d= -0.26) and trending at 120 min (p=0.08, higher, d= -0.32). The lower values in the FSD-F2R6 group were also reflected in a statistical trend for total AUC, with the placebo exhibiting a marginal elevation compared to FSD-F2R6 (p=0.06, rrb= -0.44) (Table 5).

Table 5: Vital signs AUC descriptives.

	Placebo	FSD-F2R6	rrb
Heart Rate	18,963 ± 2,797	18,268 ± 2,508[a]	-0.44
Blood Pressure (Systolic)	28,300 ± 2,162	29,389 ± 2,108*	0.89
Blood Pressure (Diastolic)	17,441 ± 1,609	17,935 ± 1,613*	0.65

Notes: *Values are reported as means ±standard deviation. All values are calculated over the entirety of the 240 min time-course. *, statistical significance ($p < 0.05$) between the groups. [a], statistical trend ($p = 0.5$-0.10) between the groups. rrb = Rank-biserial correlation between group effect size.*

Abbreviations: *AUC, area under the curve.*

Systolic and Diastolic Blood Pressure

Alcohol intoxication in all participants generally resulted in reduced systolic blood pressure (SBP). In the placebo and FSD-F2R6 treated groups, SBP was reduced from 122.5 ± 9.6 mm Hg to 118.7 ± 13.6 mm Hg, and 122.7 ± 11.3 mm Hg to 119.5 ± 14.1 mm Hg from -90 min to 0 min, respectively. Results relative to baseline values for systolic blood pressure demonstrated a significant group effect (p = 0.02), but not a significant effect for time (p=0.18), nor a significant interaction (p=0.15). Pairwise tests between groups revealed that FSD-F2R6 had higher

systolic blood pressure values than those for the placebo at 30 min (p=0.01, d=0.75), and a similar trend at 60, 120 and 240 min (p=0.06, d=0.62) (Figure 4B). Higher systolic blood pressure in FSD-F2R6 (compared to the placebo group) was reflected in a significant difference in total AUC, with FSD-F2R6 exhibiting an elevation compared to the placebo (p<0.01), with a large effect size (rrb=0.89) (Table 5). The same trends were observed in diastolic blood pressure, with results showing a significant elevation in FSD-F2R6 diastolic blood pressure AUC compared to placebo (p<0.01), with a moderate effect size (rrb=0.65) (Figure 4C and Table 5).

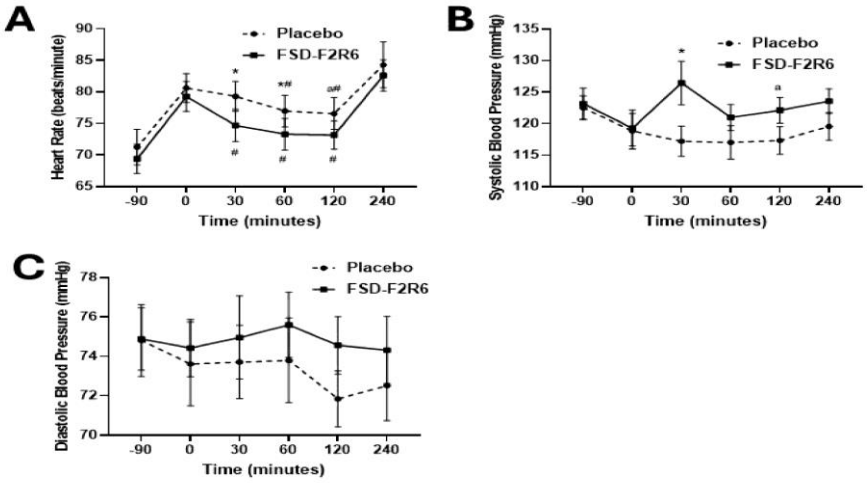

Figure 4 Physiological Changes in Heart Rate and Blood Pressure. Graphs show changes in heart rate (A), systolic blood pressure (B), and diastolic blood pressure (C) over time for participants (n=26). Values are reported as means ± SEM. *, statistical significance (p < 0.05) between the groups, within the time-point. [a], p = 0.08 (A) and p = 0.06 (B) between the groups, within the time-point. [#], p < 0.05 within the group, relative to baseline (0 min).

Oxygen saturation, Respiratory Rate, and Body Temperature

There were no significant observations made for oxygen saturation, respiratory rate, or body temperature for any participants during the study (data not reported).

Perceptual Measures

Hangover Severity

For the Single Item Hangover Severity Scale (SIHSS), there was a significant main effect for group (p=0.05) and time (p< 0.01), but not a significant interaction (p=0.34). Pairwise results within groups demonstrated that hangover symptoms declined from 8 to 24 h (p<0.05) in placebo (3.39 ± 2.86 vs. 0.92 ± 1.53) and FSD-F2R6 (2.04 ± 2.09 *vs.* 0.52 ± 1.0). Pairwise tests between groups at 8 h showed that placebo trended higher than FSD-F2R6 (p=0.06, d=0.58) (Figure 5A), and no differences between groups were observed at 24 h. Importantly, it is noted that SIHSS was 3.39 for placebo compared to 2.04 at 8 hours when FSD-F2R6 was administered—a significant decrease in hangover due to FSD-F2R6 within the 8-hour period.

We further examined hangover symptoms through the Acute Hangover Severity Scale (AHSS). Results showed that hangover symptoms declined from 8 h to 24 h. Overall, no significant group by time or between group interactions were discovered (Table 6).

Table 6 Acute Hangover Severity Scale (AHSS) assessment.

	Placebo		FSD-F2R6	
AHSS	8 hours	24 hours	8 hours	24 hours
Fatigue	4.23 ± 2.68	1.08 ± 1.61[#]	4.09 ± 2.22	1.32 ± 1.84[#]
Apathy	2.61 ± 2.76	0.52 ± 0.96[#]	2.44 ± 2.08	0.32 ± 0.75[#]
Concentration Problems	2.12 ± 2.16	0.4 ± 0.96[#]	2.59 ± 1.85	0.4 ± 0.71[#]
Clumsiness	0.96 ± 1.19	0.24 ± 0.72[#]	1.08 ± 1.08	0.16 ± 0.37[#]
Confusion	0.87 ± 1.17	0.43 ± 0.94[#]	0.52 ± 0.87	0.08 ± 0.28[#]
Thirst	4 ± 2.94	1.6 ± 1.98[#]	3.8 ± 3.01	2 ± 2.5[#]
Sweating	0.43 ± 1.27	0.04 ± 0.2[a]	0.68 ± 1.73	0.16 ± 0.47[a]
Shivering	0.5 ± 1.5	0.04 ± 0.2	0.6 ± 1.96	0.08 ± 0.4[#]
Stomach Pain	0.52 ± 1.5	0.36 ± 0.95[#]	0.72 ± 1.51	0.6 ± 1.41[#]
Nausea	1.66 ± 2.39	0.44 ± 0.82[#]	1.9 ± 2.42	0.77 ± 1.37[#]
Dizziness	1.61 ± 2.54	0.2 ± 0.58[#]	1.56 ± 2.2	0.16 ± 0.62[#]
Heart Pounding	0.52 ± 1.16	0.08 ± 0.4[#]	0.96 ± 1.95	0.12 ± 0.44[#]
Average Score	1.76 ± 1.3	0.47 ± 0.6[#]	1.72 ± 1.12	0.52 ± 0.58[#]

Notes: *Values are reported as means ± standard deviation.* [#]*, statistical significance (p < 0.05) within the group, relative.* [a]*, statistical trend (p = 0.5-0.10) between the groups, within the time-point.*

Abbreviations: *AHSS, acute hangover severity scale.*

Headache Visual Analog Scale (VAS)

Alcohol intoxication prior to ingesting a treatment resulted in elevated Headache VAS. In the placebo group, this was an increase from -90 min (0.50 ± 1.48) to 0 min (4.85 ± 11.64) and in the FSD-F2R6 group also increasing from -90 min (1.16 ± 5.03) to 0 min (4.84 ± 11.19). Results relative to baseline values for Headache VAS demonstrated a significant group-time interaction (p = 0.02). Pairwise tests between groups revealed that at 240 min, the placebo group had three-fold higher Headache VAS score than that with FSD-F2R6 (6.72 ± 10.51 and 2.20 ± 4.59, respectively) (p = 0.04, d = 0.50) (Figure 5B). Similarly, results for the 8 h subset showed that Headache VAS had a significant group-time interaction (p < 0.01). Pairwise tests within groups showed no change in headache severity in FSD-F2R6 group over time (baseline score = 4.15 ± 8.45; 8 h score = 4.33 ± 10.85); however, the placebo group experienced a significant elevation in headache VAS at 8 h (18.55 ± 22.94) relative to baseline (8.39 ± 15.64) (p = 0.02, d = 0.71). Likewise, pairwise tests between groups revealed that the placebo group had a higher Headache VAS (approximately four-fold higher) than that for FSD-F2R6 group at 8 h with a large effect size (p < 0.01, d = 0.80) (Figure 5C).

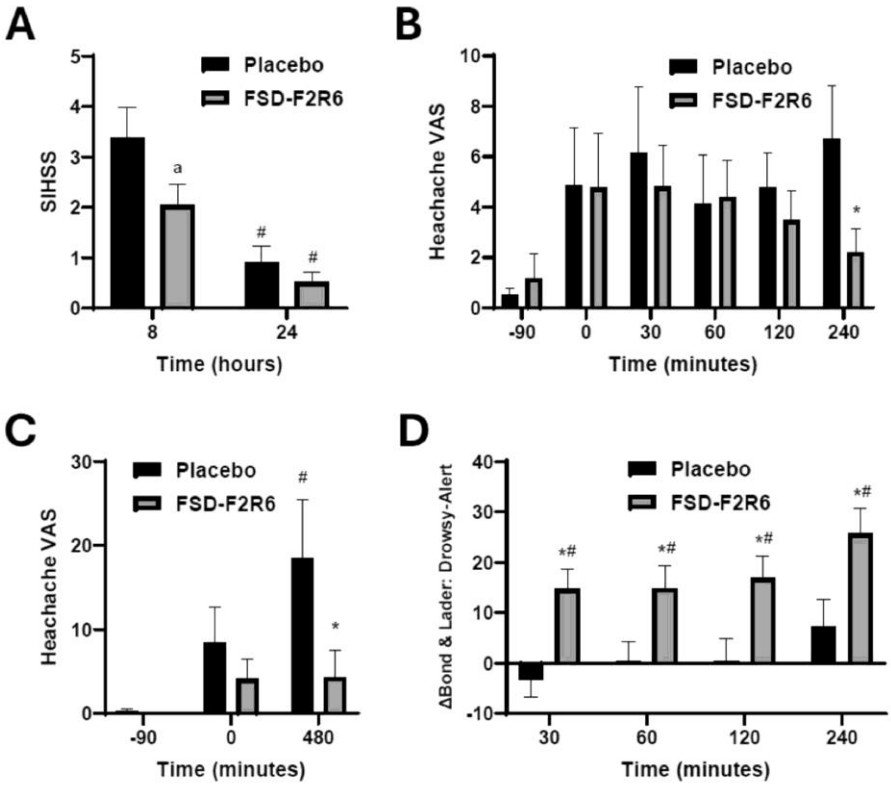

Figure 5 Perceptual changes in SIHSS (A), headache VAS at 4 h (B), headache VAS at 8 h (C) and change in Bond and Lader Drowsy-Alert (D) for all participants during the study (n=26), when placebo and FSD-F2R6 were consumed. Values are reported as means ± SEM. Bond and Lader drowsy-alert statistical analysis is on baseline centered mean data. *, statistical significance (p<0.05) within the group, relative to baseline (0 min). [#], statistical significance (p<0.05) between the groups, within the time-point. [a], p=0.06 between the groups at 8 h.

Perceived Intoxication (Intoxication VAS, Impairment VAS and Mental Fatigue VAS)

The overall state of perceived intoxication by each subject was measured using three distinct VAS scales: Intoxication VAS, Impairment VAS, and Mental Fatigue VAS.

Intoxication VAS. During -90 to 0 min, Intoxication VAS in the placebo group increased from 0.23 ± 0.86 and 66.42 ± 19.11, respectively, and in the FSD-F2R6 group also increased from 0.23 ± 0.99 to 62.65 ± 17.93, as expected. The results also indicated that Intoxication VAS for both FSD-F2R6 and placebo groups declined from 0 min to 240 min, nearly reaching pre-alcohol intoxication levels by 240 min (Table 7). There was no statistically significant difference between the two groups. It may be necessary to have a larger number of participants to capture the subjective effects reflected through such VAS analyses, due to differences in physiology among the participants or possibly some external environmental or nutritional differences.

Impairment VAS. Alcohol intoxication led to an elevated Impairment VAS, in both placebo and FSD-F2R6 groups, from -90 min to 0 min (0.69 ± 2.98 to 63.73 ± 18.14, and 0.73 ± 2.51 to 62.42 ± 17.38, respectively). There was no significant group-time interaction, nor any pairwise difference between groups collectively over the entire time-course in Impairment VAS (Table 7). However, there was a significant difference observed between the two groups in the Impairment VAS AUC changes (Table 7). The placebo group overall had a higher Impairment VAS AUC compared to that of FSD-F2R6 (7,180 ± 2,697 and 6,601 ± 3,228, respectively; $p < 0.01$), with a moderate effect size (rrb = -0.61) (Table 7). This demonstrates that the FSD-F2R6 group had better cognition and less impairment than the placebo group.

Mental Fatigue VAS. Alcohol intoxication resulted in a higher Mental Fatigue VAS, in both the placebo and FSD-F2R6 groups, from -90 min to 0 min, increasing from 4.92 ± 8.84 to 42.88 ± 25.56 and 4.35 ± 7.49 to 46.23 ± 22.58, respectively. Both groups reported similar mental fatigue prior to consuming the respective treatments. Results relative to baseline values for Mental Fatigue VAS demonstrated a trend for a group effect ($p = 0.10$), a significant time effect ($p < 0.01$), and a significant interaction ($p = 0.03$). Pairwise tests within groups demonstrated that both placebo and FSD-F2R6 treatments saw a decrease in mental fatigue as time progressed, with some exceptions. Pairwise tests between groups revealed that the placebo group had a higher Mental Fatigue VAS than that for the FSD-F2R6 group at 120 min ($p < 0.01$, $d = -0.74$), and a higher trend even at 240 min ($p = 0.09$, $d = -0.42$) (Table 7). Likewise, there was a trend for an overall lower Mental Fatigue VAS in the FSD-F2R6 group when AUCs were compared between the FSD-F2R6 group and the placebo group ($p=0.10$, $d = -0.41$) (Table 7) suggesting that FSD-F2R6, in comparison to placebo, generally led to an improvement in mental fatigue, consistently and incrementally as time progressed after consuming the treatment.

Table 7: Perception survey outcomes for Intoxication VAS, and Bond Lader VAS.

Intoxication VAS			
Intoxication	***Placebo***	***FSD-F2R6***	***d***
-90	0.23 ± 0.86	0.23 ± 0.99	0.00
0	66.42 ± 19.11	62.65 ± 17.93	-0.20
30	48.96 ± 14.2	45.32 ± 15.77	-0.26
60	34.64 ± 16.8	32.44 ± 20.94	-0.08
120	25.32 ± 15.44	24.52 ± 15.7	-0.08
240	12.28 ± 12.14$^{\#}$	8.84 ± 11.35$^{\#a}$	-0.27
AUC	7,043 ± 2,771	6,516 ± 3,219	-0.24
Impairment	*Placebo*	*FSD-F2R6*	*d*
-90	0.69 ± 2.98	0.73 ± 2.51	0.15
0	63.73 ± 18.14	62.42 ± 17.38	-0.10
30	49.36 ± 14.23$^{\#}$	46.56 ± 15.64$^{\#}$	-0.16
60	38.76 ± 21.54$^{\#}$	33.96 ± 19.46$^{\#}$	-0.25
120	25.72 ± 15.33$^{\#}$	23.36 ± 15.36$^{\#}$	-0.02
240	11.24 ± 11.79$^{\#}$	10.28 ± 12.5$^{\#}$	-0.14
AUC	7,180 ± 2,697	6,601 ± 3,228*	-0.61
Mental Fatigue	*Placebo*	*FSD-F2R6*	*d*
-90	4.92 ± 8.84	4.35 ± 7.49	-0.04
0	42.88 ± 25.56	46.23 ± 22.58	0.14
30	42.44 ± 21.31	39.28 ± 18.14$^{\#}$	-0.16
60	34.9 ± 16.8	27.88 ± 13.84$^{\#}$	-0.43
120	37.72 ± 19.36	24.24 ± 14.07$^{*\#}$	-0.74
240	24.66 ± 19.78$^{\#}$	17.84 ± 16.34$^{\#a}$	-0.42
AUC	8,369 ± 3,416	6,398 ± 2,573^{a}	-0.41
Bond and Lader			
Clearheaded - Muzzy	*Placebo*	*FSD-F2R6*	*d*
-90	4.81 ± 8.92	4.83 ± 8.83	-0.03
0	55.35 ± 19.91	53.68 ± 22.29	-0.01
30	45.64 ± 16.52$^{\#}$	46.28 ± 18.06$^{\#}$	0.08
60	37.64 ± 17.94$^{\#}$	32.2 ± 17.56$^{\#}$	-0.19
120	32.36 ± 20.58$^{\#}$	23.16 ± 18.3$^{\#}$	-0.29
240	22.84 ± 20.69$^{\#}$	14.96 ± 11.82$^{*\#}$	-0.45
AUC	8,191 ± 3,551	6,671 ± 3,131	-0.19
Clumsy - Well Coordinated	*Placebo*	*FSD-F2R6*	*d*
-90	85.65 ± 27.36	71.79 ± 39.21	-0.46

0	34.19 ± 18.33	31.92 ± 15.31	-0.16
30	45.6 ± 18.07[#]	41.32 ± 19.21[#]	-0.17
60	52.2 ± 18.25[#]	45.52 ± 22.85[#]	-0.39
120	59.8 ± 22.6[#]	53.32 ± 26.84[#]	-0.28
240	74.16 ± 22.12[#]	71.04 ± 24.24[#]	-0.05
AUC	14,052 ± 3,647	12,765 ± 4,438	-0.10
Energetic - Lethargic	*Placebo*	*FSD-F2R6*	*d*
-90	17.19 ± 20.29	22.21 ± 23.65	0.16
0	35.77 ± 20.52	38.96 ± 25.4	0.16
30	41.88 ± 17.82	40.76 ± 17.87	0.02
60	39.72 ± 18.39	30.2 ± 17.99[a]	-0.42
120	40.64 ± 19.98	34.64 ± 21.89	-0.24
240	40.8 ± 25.66	28.96 ± 22.52[a]	-0.44
AUC	9,691 ± 3,824	8,012 ± 3,672	0.01
Drowsy - Alert	*PLA*	*FSD-F2R6*	*d*
-90	73.85 ± 28.87	68.29 ± 31.56	-0.18
0	49.73 ± 19.6	37.96 ± 25*	-0.59
30	46.16 ± 17.36	52.68 ± 19.48[#]^	0.38
60	50.2 ± 18.57	52.8 ± 22.01[#]^	0.14
120	50.16 ± 22.04	54.8 ± 22.33[#]^	0.24
240	56.96 ± 27.43	63.64 ± 24.66[#]^	0.32
AUC	12,329 ± 3,670	13,252 ± 3,571	0.03
Mentally Slow - Quick Witted	*Placebo*	*FSD-F2R6*	*d*
-90	83.31 ± 18.11	79.67 ± 24.9	-0.17
0	45.42 ± 21.44	40.96 ± 17.31	-0.29
30	45.24 ± 12.35	48.28 ± 19.14	0.10
60	52.64 ± 16.69	54.96 ± 21.46[#]	0.05
120	57.92 ± 15.96[#]	60.36 ± 19.19[#]	0.15
240	69.28 ± 20.43[#]	68.76 ± 21.54[#]	0.10
AUC	13,774 ± 3,075	14,154 ± 3,560	-0.40

Notes: *Values are reported as means ±standard deviation. [#], statistical significance ($p < 0.05$) within the group, relative to baseline (0 min); *, $p < 0.05$ between the groups, within the time-point; [a], statistical trend between the groups ($p = 0.5$-0.10) within the time-point; ^, significantly different between groups after baseline centered mean analysis; d ,Cohen's d between group effect size.*

Abbreviations: *AUC, area under the curve; VAS, visual analog scale.*

Bond and Lader VAS

Clearheaded–Muzzy. Alcohol intoxication (prior to treatment) resulted in elevated Bond and Lader score for Clearheaded-Muzzy, indicating participants were more Muzzy (less clearheaded). The placebo group demonstrated an increase from -90 min (4.81 ± 8.92) to 0 min (55.35 ± 19.91) with the FSD-F2R6 group also increasing from -90 min (4.83 ± 8.83) to 0 min (53.68 ± 22.29). Results relative to baseline values for Clearheaded-Muzzy demonstrated a significant time effect ($p < 0.01$), but not a significant interaction ($p = 0.20$). Pairwise tests within groups demonstrated a statistically significant, and a linear decrease over time at each timepoint for both treatment groups. Pairwise differences between groups revealed that the placebo group had a higher Clearheaded-Muzzy score (i.e. less clearheaded) than FSD-F2R6 at 240 min ($p = 0.05$, $d = -0.45$) (Table 7).

Clumsy–Well Coordinated. Intoxication (prior to treatment) resulted in a reduced Bond and Lader score for Clumsy–Well Coordinated behavior, indicating reduced perceived coordination (i.e. higher clumsy score). The placebo group demonstrated a decrease from -90 min (85.65 ± 27.36) before alcohol administration to 0 min (34.19 ± 18.33) and the FSD-F2R6 group also demonstrated a decrease from -90 min (71.79 ± 39.21) to 0 min (31.92 ± 15.31) (Table 7). Results relative to baseline values for Clumsy–Well Coordinated demonstrated a trend for a group effect ($p = 0.09$), a significant time effect ($p < 0.01$), but no interaction ($p = 0.72$). Pairwise tests within groups demonstrated a statistically significant and linear increase over time at each timepoint for both treatment groups. No significant differences were found between groups.

Energetic–Lethargic. Intoxication (prior to treatment) resulted in elevated Bond and Lader score for Energetic–Lethargic, indicating participants were more Lethargic (less energetic), with placebo and FSD-F2R6 both showing increases from -90 min (17.19 ± 20.29) to 0 min (35.77 ± 20.52) and from -90 min (22.21 ± 23.65) to 0 min (38.96 ± 25.4) respectively. Results relative to baseline values for Energetic–Lethargic demonstrated a

main effect for time (p = 0.11), and a significant interaction (p = 0.04). Pairwise differences between groups revealed that the placebo group tended to have a higher Energetic–Lethargic score (meaning more lethargic) than FSD-F2R6 at 60 (p =0.06, d = -0.42), and 240 min (p = 0.06, d = -0.44) (Table 7).

Drowsy–Alert. Intoxication (prior to treatment) resulted in a reduced Bond and Lader score for Drowsy–Alert, indicating participants were more drowsy (hence less alert), with the placebo group demonstrating a decrease from -90 min (73.85 ± 28.87) to 0 min (49.73 ± 19.6) and the FSD-F2R6 group also demonstrating a decrease from -90 min (68.29 ± 31.56) to 0 min (37.96 ± 25). Results relative to baseline values for Drowsy–Alert demonstrated a significant effect for time (p < 0.02), and a significant interaction (p = 0.02). Pairwise differences within groups demonstrated that FSD-F2R6 significantly increased alertness from baseline in a linear fashion at all time points (p < 0.05). Conversely, there were no significant differences throughout the time-course in the placebo group. Pairwise differences between groups demonstrated that baseline values were significantly higher in the placebo group than the FSD-F2R6 group. Therefore, we conducted an additional analysis on baseline centered means at baseline. After baseline centering, pairwise tests between groups demonstrated significant differences at all time-points including at 30, 60, 120, and 240 min (Figure 5D, Table 7) with FSD-F2R6 treatment showing greater alertness.

Mentally Slow–Quick Witted. Intoxication (prior to treatment) resulted in reduced Bond and Lader score for Mentally Slow–Quick Witted, indicating participants were more mentally slow (less quick witted). Placebo and FSD-F2R6 participants showed a decrease from -90 min (83.31 ± 18.11) to 0 min (45.42 ± 21.44) and from -90 min (79.67 ± 24.9) to 0 min (40.96 ± 17.31) respectively. There were no group, or group by time interactions. Overall, results showed that both treatments increased linearly overtime (become more quick-witted), with no significant differences between treatments (Table 7).

Cognitive and Motor Tests

Trail Making Test (TMT)

Trail 1. Intoxication (prior to treatment) resulted in elevated Trail 1 Errors, with the placebo group showing an increase from -90 min (0.31 ± 0.55) to 0 min (0.81 ± 0.9) and the FSD-F2R6 group also increasing from -90 min (0.62 ± 1.27) to 0 min (1.12 ± 1.37). Likewise, there was an increase in Trail 1 Time (measured in seconds), with placebo showing an increase from -90 min (37.19 ± 8.65) to 0 min (37.57 ± 9.30) and FSD-F2R6 treatment showing an increase from -90 min (40.89 ± 11.23) to 0 min (41.95 ± 11.73). Results relative to baseline values for TMT Trail 1 Errors demonstrated a significant main effect for time effect (p < 0.01) and a trend for significant interaction (p = 0.06). Pairwise tests within groups demonstrated more consistent decreases over time with FSD-F2R6 treatment, with significant declines from baseline at 60, 120, and 240 min (p < 0.05 at all time points). Whereas, for the placebo group, there were no statistically significant differences, only 120 min tended to be lower than baseline (p = 0.10). Pairwise tests between groups demonstrated that placebo was significantly higher (i.e. more cognitive and motor errors) than FSD-F2R6 at 60 min (p = 0.01, d = -0.55). Similarly, the results for the time to complete TMT Trail 1 relative to baseline demonstrated a significant time effect (p < 0.01), and a significant interaction (p = 0.01). Pairwise tests within groups demonstrated more consistent decreases over time with FSD-F2R6, with significant linear decreases at all timepoints relative to baseline (p < 0.05), whereas the placebo group demonstrated a delayed reduction, and was only significantly lower than baseline at 60, 120, and 240 min. Pairwise tests did not show significant differences between groups (Table 8).

Trail 2. Like Trail 1, intoxication (prior to treatment) resulted in elevated errors and time to complete Trail 2. However, statistically there were no group by time interactions, or between group differences (Table 8).

Table 8: Results of the trail making tests (Trail 1 and Trail 2).

Trail 1 Errors (Total)	***Placebo***	***FSD-F2R6***	***d***
-90	0.31 ± 0.55	0.62 ± 1.27	0.23
0	0.81 ± 0.9	1.12 ±1.37	0.20
30	0.84 ± 0.99	0.72 ± 0.98	-0.18
60	0.88 ± 1.17	0.28 ± 0.68$^{*\#}$	-0.55
120	0.32 ± 0.75	0.4 ± 0.82$^{\#}$	0.11
240	0.64 ± 1.44	0.28 ± 0.61$^{\#}$	-0.20
Trail 1 Time (ms)	*Placebo*	*FSD-F2R6*	*d*
-90	37,197 ± 8,656	40891 ± 11,231	0.38
0	37,571 ± 9,308	41,955 ± 11,738	0.35
30	35,964 ± 9,825	37,310 ± 11,977$^{\#}$	0.03
60	33,521 ± 10,281$^{\#}$	33,527 ± 12,359$^{\#}$	-0.12
120	30,122 ± 8,241$^{\#}$	32,031 ± 10,278$^{\#}$	0.08
240	31,398 ± 8,490$^{\#}$	29,715 ± 7,590$^{\#}$	-0.28
Trail 2 Errors (Total)	*Placebo*	*FSD-F2R6*	*d*

-90	1.23 ± 1.63	1.81 ± 2.08	0.28
0	3.13 ± 2.19	3.42 ± 2.85	0.03
30	2.04 ± 1.93[#]	1.8 ± 2.29[#]	-0.17
60	2 ± 2.27[#]	2.3 ± 2.75	0.19
120	1.24 ± 1.59[#]	0.88 ± 1.17[#]	-0.24
240	0.52 ± 0.82[#]	1.06 ± 1.86[#]	0.31
Trail 2 Time (ms)	*Placebo*	*FSD-F2R6*	*d*
-90	48,915 ± 16,340	55,217 ± 21,698	0.27
0	56,689 ± 16,452	57,175 ± 21,815	0.04
30	44,017 ± 12,533[#]	46,679 ± 19,332[#]	-0.01
60	42,208 ± 13,676[#]	47,415 ± 23,057[#]	0.07
120	40,039 ± 13,518[#]	38,870 ± 13,077[#]	-0.14
240	34,641 ± 9,846[#]	37,991 ± 14,749[#]	0.06

Notes: *Values are reported as means ±standard deviation for all participants (n=26). [#], p < 0.05 within the group relative to baseline at 0 min; *, p < 0.05 between the groups within the time-point; [a], statistical trend between the groups within the time point, p = 0.5-0.10; d = Cohen's d between group effect size.*

Abbreviations: *ms, milliseconds.*

DRUID Score

The DRUID app was used to assess cognitive and motor impairment related to intoxication, generating a single impairment score.[10] Overall, results demonstrated a linear reduction in DRUID score over time from baseline at 0 min within both treatment groups. However, there were no significant group by time interactions, or pairwise differences found between treatment conditions, suggesting no significant effect of treatment on DRUID score (Table 9). This suggested that the treatment did not influence cognition and coordination in a significant way. This lack of significant change potentially highlights the app's limited ability to capture treatment effects in this study, making it less reliable for evaluating intervention outcomes in the context of cognitive and motor impairment due to alcohol. The app, however, was effective in detecting impairment but did not demonstrate sensitivity to treatment-related improvements, when compared to other assessments used in this study.

Table 9: Cognitive and motor test outcomes.

DRUID Score	***Placebo***	***FSD-F2R6***
-90	41.24 ± 5.06	41.69 ± 3.87
0	50.9 ± 11.48	52.24 ± 11.79
30	44.46 ± 5.42[#]	47.7 ± 9.86[#]
60	43.71 ± 6.22[#]	44.15 ± 8.06[#]
120	42.41 ± 7.22[#]	41.77 ± 5.52[#]
240	41.46 ± 4.84[#]	41.06 ± 5.37[#]
DSST		
DSST-Correct Responses (Total)	***Placebo***	***FSD-F2R6***
-90	59.58 ± 13.03	59.23 ± 16.86
0	59 ± 12.86	59.38 ± 19.71
30	67.16 ± 15.79[#]	65.96 ± 21.5[#]
60	71.2 ± 18.26[#]	71.88 ± 20.49[#]
120	74.64 ± 19.01[#]	77.8 ± 19.36[#]
240	78.32 ± 18.78[#]	80.92 ± 22.49[#]
DSST Response Time (seconds)	***Placebo***	***FSD-F2R6***
-90	2.11 ± 0.48	2.2 ± 0.66
0	2.13 ± 0.5	2.25 ± 0.77
30	1.9 ± 0.53[#]	2.03 ± 0.73[#]
60	1.83 ± 0.64[#]	1.8 ± 0.5[#]
120	1.73 ± 0.52[#]	1.65 ± 0.47[#]
240	1.63 ± 0.47[#]	1.63 ± 0.62[#]

Notes: *Values are reported as means ±standard deviation. [#], statistical significance (p < 0.05) within the group.*

Abbreviations: *DSST, digit symbol substitution task.*

Digit Symbol Substitution Test (DSST)

Overall, there was no change in the DSST correct responses, or total response time from -90 min to 0 min. Statistically, participants committed no errors; thus, we were unable to examine this endpoint. Overall, these results indicate that intoxication did not have an impact

on DSST outcomes, making it likely an inappropriate outcome metric for this study design. Further, there were no group by time differences, or pairwise differences between groups, suggesting no impact of treatment on DSST score. There was, however, a linear increase in correct responses over the time-course compared to baseline at 0 min and a decrease in errors. Since there was no evidence that intoxication impacted these scores, we interpret this as a possible learning effect from repeating the test over time (Table 9).

Safety Outcomes

Urinalysis

Urinalysis results showed that all parameters were within normal limits prior to study participation and at the 24 h post-test follow up session for both study treatments (data not reported).

Blood Analyses

Blood analyses were primarily conducted to understand any variations and safety concerns in various markers at baseline, after the consumption of FSD-F2R6 and placebo. All data were consistent and there were no variations from the baseline as described below.

Complete Blood Count (CBC). All CBC data were within normal limits at baseline and at 24 h post-test, for both treatment groups. There were no reported differences between the two treatments. There were noted changes within groups from baseline, however. There was a significant effect for white blood cell count (WBC), with placebo being elevated compared to baseline values ($p < 0.05$) (baseline = 6.04 ± 1.53; placebo = 6.65 ± 1.99), with a small effect size ($d = 0.23$). There was also a statistical trend for neutrophil numbers to be higher in placebo compared to baseline values ($p = 0.09$) (baseline = 3.52 ± 1.35; placebo = 4.06 ± 1.78), with a small effect size ($d = 0.25$). No other significant differences were found in CBC analysis (Table 10).

Comprehensive metabolic panel (CMP). All CMP blood parameters were within normal limits at baseline and at 24 h post-test, for both treatment groups. There were two reported differences between the two treatments, as well as several changes within groups from baseline. Blood urea nitrogen (BUN) was lower for both FSD-F2R6 and placebo 24 h post-test compared to baseline ($p = 0.03$ for FSD-F2R6, $p = 0.01$ for placebo) (baseline=12.88 ± 3.51; placebo=11.39 ± 3.23; FSD-F2R6 =11.46 ± 2.73), with small effect sizes (0.47 and 0.42, for placebo and FSD-F2R6, respectively). There were no other differences between treatments. Likewise, the BUN/creatinine Ratio was also reduced, and significantly lower in FSD-F2R6 ($p < 0.01$) and placebo ($p = 0.03$) at 24 h post-test compared to baseline (baseline=15.62 ± 4.26; placebo=13.93 ± 3.61; FSD-F2R6 =13.64 ± 3.96), with small effect sizes (0.41 and 0.44, for placebo and FSD-F2R6, respectively).

Albumin protein for placebo was reduced compared to baseline ($p = 0.01$), and to FSD-F2R6 ($p = 0.04$) (baseline=4.53 ± 0.27; placebo=4.4 ± 0.29; FSD-F2R6 =4.51 ± 0.30), with small effect sizes ($d = 0.44$ for placebo from baseline, and 0.35 between placebo and FSD-F2R6). No other significant differences were found in CMP analysis (Table 10).

Fibrinogen. No significant differences were found within or between treatments as compared to baseline values. All values were within normal limits.

Table 10: Blood analysis results.

	Baseline (0 h)	Placebo (24 h)	FSD-F2R6 (24 h)
WBC (K/uL)	6.04 ± 1.53	6.65 ± 1.99[#]	6.45 ± 1.88
RBC (M/uL)	4.72 ± 0.45	4.72 ± 0.48	4.78 ± 0.53
Hemoglobin (g/dL)	13.92 ± 1.44	13.82 ± 1.46	14.06 ± 1.58
Hematocrit (%)	42.43 ± 4.17	42.09 ± 4.41	43.12 ± 4.51
MCV (fl)	89.96 ± 4.82	89.21 ± 4.8	90.6 ± 5.13
MCH (pg)	29.48 ± 1.65	29.31 ± 1.85	29.5 ± 1.92
MCHC (g/dL)	32.8 ± 0.79	32.85 ± 0.84	32.63 ± 0.85
RDW (%)	12.73 ± 1	12.7 ± 1.08	12.71 ± 1.1
Platelet Count (K/uL)	288.88 ± 55.11	297.08 ± 58.3	297.16 ± 58.93
Neutrophil (%)	56.81 ± 8.24	58.96 ± 9.64	57.28 ± 9.28
Lymphocyte (%)	32.62 ± 8	31.25 ± 8.69	32.48 ± 8
Monocyte (%)	7.73 ± 1.69	7.17 ± 1.46	7.6 ± 1.78
Eosinophil (%)	2 ± 1.06	1.83 ± 1.17	1.72 ± 1.17
Basophil (%)	0.73 ± 0.53	0.71 ± 0.46	0.84 ± 0.47
Neutrophil (#)	3.52 ± 1.35	4.06 ± 1.78	3.82 ± 1.7
Lymphocyte (#)	1.9 ± 0.49	1.96 ± 0.43	1.99 ± 0.47
Monocyte (#)	0.47 ± 0.15	0.48 ± 0.13	0.47 ± 0.13
Eosinophil (#)	0.12 ± 0.07	0.13 ± 0.08	0.12 ± 0.08
Basophil (#)	0.04 ± 0.05	0.03 ± 0.05	0.04 ± 0.05
Glucose (mg/dL)	85.65 ± 10.01	85.91 ± 10.29	85 ± 9.5
BUN (mg/dL)	12.88 ± 3.51	11.39 ± 3.23[#]	11.46 ± 2.73[#]

Creatinine (mg/dL)	0.84 ± 0.16	0.82 ± 0.15	0.87 ± 0.17
GFR (mL/min)	101.65 ± 17.13	103.13 ± 16.45	99.83 ± 16.88
BUN/Cre Ratio	15.62 ± 4.26	13.93 ± 3.61[#]	13.64 ± 3.96[#]
Sodium (mmol/L)	138.96 ± 2.42	137.78 ± 1.78[#]	138.75 ± 1.54[a]
Potassium (mmol/L)	4.4 ± 0.22	4.33 ± 0.23	4.46 ± 0.39
Chloride (mmol/L)	102.54 ± 2.06	101.61 ± 1.56	101.88 ± 2.15
CO2 (mmol/L)	22.92 ± 1.74	22.74 ± 1.89	23.04 ± 1.83
Calcium (mg/dL)	9.57 ± 0.41	9.4 ± 0.40	9.53 ± 0.37
Total Protein (g/dL)	7.19 ± 0.33	7.03 ± 0.48	7.12 ± 0.44
Albumin (g/dL)	4.53 ± 0.27	4.4 ± 0.29[#]	4.51 ± 0.30*
Globulin (g/dL)	2.65 ± 0.25	2.63 ± 0.33	2.61 ± 0.29
Bilirubin (mg/dL)	0.63 ± 0.36	0.65 ± 0.40	0.73 ± 0.42
Alkaline Phosphatase U/L)	67.54 ± 22.62	68.39 ± 23.42	64.88 ± 20.17
AST (U/L)	20.58 ± 6.52	20 ± 5.32	20.71 ± 4.53
ALT (U/L)	18.85 ± 9.26	18.35 ± 9.08	18.17 ± 8.65
Albumin/Globulin Ratio	1.72 ± 0.2	1.7 ± 0.22	1.75 ± 0.22
Fibrinogen Activity (mg/dL)	321.23 ± 86.66	313.78 ± 83.99	301.92 ± 73.46

Notes: *Values are reported as means ±standard deviation. [#], statistical significance ($p < 0.05$) within the group, relative; *, statistical significance ($p < 0.05$) between the groups within the time-point; [a], statistical trend ($p = 0.5$-0.10) between the groups within the time-point.*

Abbreviations: *ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; h, hours; MCH, mean corpuscular hemoglobin; GFR, glomerular filtration rate; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.*

Adverse Events

Five adverse events were reported in the trial, four occurring in placebo, and one occurring in FSD-F2R6. Two participants – one female subject in the FSD-F2R6 group and one male subject in the placebo group, experienced nausea and vomiting, which occurred shortly after administration of the test treatments (in the intoxicated state). The subject in placebo also experienced a headache. Both participants stabilized, and symptoms resolved.

One female subject in the placebo group complained of severe headache at 4 h post treatment, which resolved over time. Another female subject in the placebo group complained of a migraine that lasted more than 30 min and began after ingestion of the study (placebo) treatment in the intoxicated state. One female subject in the placebo group reported vaginal bleeding in the evening several hours after completion of the study event, which was believed to be unrelated to study treatment and due to the start of her menstrual period. Overall, no serious adverse events were reported for this study.

DISCUSSION

In this study, treatment with either FSD-F2R6 or placebo began after alcohol consumption was completed, and BAC had reached a peak level. Here, we show that FSD-F2R6 enhanced the metabolism of alcohol (as measured by BAC reductions and alcohol AUC reductions) when compared with placebo. FSD-F2R6 was also significantly associated with stabilization of alcohol-induced heart rate and blood pressure changes, a reduction of symptoms of intoxication, an improvement in cognition as measured by the Trail Making Test, less mental fatigue, more alertness more clear-headedness, and a significant reduction in hangover symptoms as measured by a headache VAS. Hangover severity, as measured by the Single Item Hangover Severity Scale (SIHSS) trended lower for FSD-F2R6 at 8 hours compared to placebo. The FSD-F2R6 formulation was also found to be safe with no serious adverse events in the trial, and no adverse events specific to treatment with FSD-F2R6.

A unique element in the design of this clinical trial was that the treatment (FSD-F2R6 or placebo) was not administered to participants until a peak alcohol level had been achieved. This was accomplished by having participants wait for a period of time after ingesting the alcohol and performing serial breathalyzer measurements. With such a design, one could better focus on elimination of alcohol from the body instead of confounding data due to the continued absorption of alcohol from the stomach and intestinal tract. The study design also mirrored a real-life situation in which an individual would take FSD-F2R6 after consuming alcohol and after reaching an inebriated state. This is opposed to being required to consume FSD-F2R6 either before or immediately after consuming an alcoholic beverage. The current trial also targeted a BAC of 0.07 to 0.10%, a level at which participants would perceive themselves to be intoxicated, display a measurable drop in cognitive function, and develop hangover symptoms. An additional strength is the heterogeneity of the study

population including a wide age range and mixed ethnicities.

Based on paired data from all participants, FSD-F2R6 significantly lowered BAC levels compared with placebo (Table 4). This occurred as early as 30 min post-treatment and continued through the 4 h timepoint. Further analysis revealed that most participants (70%) were rapid responders to FSD-F2R6 with an average 40% increase in alcohol metabolism in the first 30 minutes, when compared with placebo (Figure 3).

There are likely multiple mechanisms by which FSD-F2R6 accelerated the removal of alcohol from the body. One of the ingredients in the formulation is Dihydromyricetin (DHM), which is shown to enhance alcohol metabolism. DHM is a naturally occurring flavonoid found in *Hovenia dulcis*, and *Ampelopsis grossedentata*.[14,15] In mice, DHM was shown to prevent ethanol-induced liver injury, an effect that was associated with increased expression of ethanol-metabolizing enzymes and reduced ethanol and acetaldehyde concentrations. Fructose is another ingredient with alcohol-reducing properties. The effect of fructose in accelerating alcohol metabolism has been studied since the 1950's with positive results reported.[16] Fructose has been associated with lower blood alcohol levels and increased alcohol metabolism in humans at varying doses, ranging from 0.25 to 1 g/kg.[16,18] There are also various B vitamins (B_1, B_2, B_3, B_6 and B_{12}) included in the FSD-F2R6 treatment, among which vitamin B_3 has a direct role in increasing NAD+ concentrations required for the oxidative metabolism of ethanol and acetaldehyde. Other vitamins are included for general nutritional support and to potentially increase energy levels post alcohol consumption.

FSD-F2R6 was also effective at reversing trends in blood pressure reduction and heart rate elevation, both of which are common following alcohol consumption. Alcohol is known to induce peripheral vasodilation and can lower both systolic and diastolic blood pressure even after moderate intake.[19] Heart rate increases are also observed following alcohol intake and likely occur in response to peripheral vasodilation and dehydration. In this trial, we found that FSD-F2R6 stabilized blood pressure and prevented heart rate increases following alcohol intake. Although these changes may be related to the BAC lowering effects of FSD-F2R6, they may also be related to the caffeine in the FSD-F2R6 formulation, as caffeine is known to cause transient elevations in blood pressure.[20,21] Caffeine is thought to raise blood pressure by blocking the action of adenosine, a molecule that promotes peripheral vasodilation and can lower blood pressure. By counteracting alcohol-induced vasodilation, caffeine may also have prevented the reflexive heart rate increase that occurs following alcohol ingestion. Methylliberine, a xanthine that is structurally related to caffeine, may also have prevented an alcohol-induced drop in blood pressure as it is thought to have a similar mechanism of action to caffeine. However, methylliberine was not found to influence blood pressure and heart rate.[22]

Based on self-report measures and the Trail Making Tests, FSD-F2R6 was effective at enhancing mental alertness and improving cognition post-alcohol consumption. The Drowsy-Alert VAS, for example, showed significant improvement as soon as 30 min post-treatment with FSD-F2R6, and this effect persisted throughout the 4 h observation period. There were also significant improvements in the Impairment VAS by AUC in the 4 h period. In terms of improvement in cognition, FSD-F2R6 was associated with less type 1 errors in the Trail Making Test at 60 min and more consistent decreases in errors over time than with placebo. Alcohol is known to decrease alertness and induce mental confusion, an effect that is thought to be due to disruption of the balance of inhibitory and excitatory neurotransmitters tilting the balance in favor of inhibitory influences.[23,24] One of the main targets for alcohol in the central nervous system is the GABA-A receptor where it can potentiate the activity of the inhibitory neurotransmitter GABA.[25] Multiple ingredients in FSD-F2R6 could have contributed to the ability of this treatment to increase mental alertness in this trial. In addition to its ability to lower blood alcohol levels.[26,28] DHM has been shown to interact with the GABA-A receptors in the central nervous system to block alcohol-induced potentiation of GABA-A signaling.[29,30] While not directly blocking the effects of alcohol, other ingredients such as caffeine and methylliberine would have also improved mental alertness in the intoxicated state. Caffeine has been shown to be effective in improving cognitive performance, alertness and wakefulness, mental sharpness, physical energy, and motor performance.[31] Methylliberine is a synthetic purine alkaloid that has been shown to improve alertness alone and in combination with caffeine and theacrine.[22] Interestingly, methylliberine may potentiate the effects of caffeine, allowing for lower does of caffeine in products while maintaining the same ability to promote alertness.[32] Another ingredient in FSD-F2R6, huperzine A, may also have contributed to improved cognition. Huperzine A, a compound isolated from *Huperzia serrata*, is a selective, reversible inhibitor of acetylcholine esterase (AChE) with neuroprotective and memory enhancing properties.[33] Although it has not been tested in acute alcohol intoxication previously, Huperzine A has demonstrated a positive effect on cognitive function in Alzheimer's disease and vascular dementia patients in clinical trials.[34,35]

Finally, treatment with FSD-F2R6 resulted in a reduction of the symptoms of alcohol-induced hangovers. The cause of hangovers is thought to be multifactorial resulting from inflammation, oxidative damage and toxic breakdown products of alcohol, specifically acetaldehyde.[36,37] DHM, which is present in FSD-F2R6,

is present in many hangover remedies with clinical trials demonstrating efficacy in alleviating the symptoms of alcohol-induced hangovers. DHM is thought to prevent hangovers via its anti-inflammatory effects and enhancement of acetaldehyde metabolism.[38] Additional antioxidants in the FSD-F2R6 formulation including isoquercitrin, milk thistle (silymarin) and huperzine A may also have helped mitigate hangovers post-alcohol ingestion. Isoquercitrin, an ingredient used in FSD-F2R6, is converted into quercetin in the body.[39] Quercetin is a commonly occurring polyphenolic bioflavonoid typically found in grapes, wine, green tea, apples, onions, and green leafy vegetables.[40] Quercetin has been shown to be beneficial in animal studies, demonstrating anti-inflammatory, anti-carcinogenic, antioxidant, and immune modulation effects.[41,44] This compound was reported to show a protective effect on ethanol-induced acute liver injury via the upregulation of protective liver enzymes, increase of antioxidant activity against oxidative stress, and reduced expression of proinflammatory cytokines.[45] Milk thistle extract is a complex mixture of phytochemicals, and silymarin is an active extract with flavonolignans extracted from the milk thistle, *Silybum marianum (L.) gaernt.*[46] This component is a very popular substance in many natural product formulations. Milk thistle extract can function as a free radical scavenger and modulator of enzymes involved in cellular damage, fibrosis and cirrhosis.[21] potentially countering the ethanol-derived free radicals in hepatocytes.[47,48]

There are several limitations of this study. Notably, BAC was not measured post-treatment using blood samples. The study was designed this way given prior studies that consistently demonstrate an excellent correlation between BAC measured from blood and BAC calculated using a breathalyzer.[4,5] A significant reduction in hangover symptoms was also recorded. This suggests that FSD-F2R6 lowered the levels of ethanol and potentially its metabolite, acetaldehyde, in the system faster than placebo, although this would need to be confirmed in additional studies. It is reported that a faster ethanol elimination rate is associated with less severe hangovers, especially in the first hours after alcohol consumption.[45] and the current clinical study with FSD-F2R6 confirms this association as well. It is important to note that DHM, an ingredient in FSD-F2R6, has been experimentally shown to lower acetaldehyde in mice following treatment with alcohol.[49] In future studies, these types of serum biomarkers could provide additional details about the mechanisms by which FSD-F2R6 reduces the adverse effects of alcohol. It is interesting to note that data analysis suggests that males and females responded similarly to FSD-F2R6; however, this would need to be confirmed in a further study with a larger number of participants.

It is advised, as a precautionary measure, that people with a history of cardiovascular conditions such as hypertension, tachycardia and cardiac arrhythmias, phenylketonuria or a history of seizures should seek medical advice before consuming FSD-F2R6. It is recommended that FSD-F2R6 not be administered to pregnant females, lactating females, children, or the elderly given the lack of safety evidence for individual ingredients in these populations.

FSD-F2R6 is a formulation of dietary supplements and vitamins that was established with the following functions to treat and reverse acute alcohol intoxication: 1. acceleration of alcohol metabolism, 2. improvement of mental alertness and cognitive function, 3. reduction of hangover symptoms, and 4. general nutritional support. In this randomized, placebo controlled, crossover trial, FSD-F2R6 was shown to lower BAC levels faster when compared with placebo. FSD-F2R6 was also associated with the reversal of alcohol-induced heart rate and blood pressure changes, self-reported symptoms of intoxication, improvement in cognition as measured by the Trail Making Test (TMT), a reduction in mental fatigue, an increase in alertness and clear-headedness, and a reduction in hangover symptoms as measured by a headache VAS. These effects may be related to the ability of FSD-F2R6 to lower BAC or may be independent (e.g., caffeine can raise blood pressure by adenosine antagonism). Although several adverse events were observed in this trial, these events appear to be related to alcohol intake rather than FSD-F2R6 treatment effects, as all but one event occurred in the placebo group. These data suggest that FSD-F2R6 is safe and may be useful in mitigating the acute effects of alcohol intoxication. Further studies are needed to define the mechanisms by which the FSD-F2R6 formulation counters the intoxicating properties of alcohol.

CONCLUSIONS

FSD-F2R6 is a proprietary dietary supplement formulated for use as a non-medical intervention to reverse the immediate effects of alcohol consumption and acute alcohol intoxication. This formulation resulted in a clinically significant improvement of mental alertness, improved cognition, stabilization of blood pressure and heart rate, and acceleration of alcohol elimination from the body when compared to placebo in this study. It should also be mentioned that several participants in this study noted a marked difference between the placebo and FSD-F2R6 treatment sessions, with many of them surmising correctly when they were receiving FSD-F2R6. This suggests that there were conscious, noticeable physical and mental differences due to FSD-F2R6.

The product is intended to treat alcohol intoxication by accelerating ethanol metabolism, improving mental alertness and reducing hangover symptoms, compared with placebo. Treatment with FSD-F2R6 led to significant reductions in BAC as early as 30 min and a significant reduction in the alcohol AUC. In addition, it was found that 70.8% (17/24) of the most rapidly responding participants had an average 40% greater

BAC% decrease with FSD-F2R6 at 30 min when compared to placebo. It is worth noting that individual responses to alcohol can vary, and such individual variations in alcohol metabolism (including, for example, genetic factors, nutritional status and sex) may influence the effect of FSD-F2R6. Treatment with FSD-F2R6 significantly improved cognition, alertness, clear-headedness, mental clarity, energy and other symptoms of alcohol intoxication, as early as 30 min post-treatment. There were fewer cognitive and motor errors with FSD-F2R6 compared with placebo. FSD-F2R6 significantly reduced hangover symptoms at 4- and 8-hours post-treatment, as measured by a headache VAS. Hangover severity, as measured by the Single Item Hangover Severity Scale (SIHSS) trended lower for FSD-F2R6 at 8 hours compared to placebo The administration of a placebo to alcohol-intoxicated individuals in the current study did not mitigate changes in the hemodynamic effects of alcohol such as elevated heart rate and reduced blood pressure (both systolic and diastolic BP). The FSD-F2R6 formulation attenuated these effects in a statistically significant fashion when compared to the placebo. There were no serious adverse events in the trial.

FSD-F2R6 is a safe and effective dietary supplement clinically proven to significantly and efficiently mitigate the immediate effects of excess alcohol consumption by reducing BAC, significantly improving cognition, and reducing hangover effects.

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