Original Research

ASSESSING THE EFFECTIVENESS OF PROANECY HEPA MILK FOR PREVENTING AN INCREASE OF BLOOD ETHANOL CONCENTRATION

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ABSTRACT

Aims: This study aimed to investigate whether consuming 6ml/kg of Proanecy Hepa milk prior to alcohol consumption could limit the increase in blood alcohol concentration (BAC).

Methods: A self-controlled clinical trial with 6 ethanol pharmacokinetic crossover trials was performed. Ten fasting students were divided into six groups, each receiving different substances before consuming 0.5g of ethanol/kg. The substances administered included Pure water, Alcohol antidote, Proanecy Hepa milk, Proanecy Hepa milk without Silymarin, Silymarin, and Liver support milk. BAC was measured at five-time points using gas chromatography: baseline (t_0), 60 minutes (t_1), 120 minutes (t_2), 180 minutes (t_3), and 240 minutes (t_4) after alcohol intake. iAUC of blood ethanol were presented as median (interquartile range).

Results: The group that consumed Proanecy Hepa demonstrated a significantly lower increase in BAC, as indicated by the incremental area under the curve (iAUC) (170.9, 50.5–470.8), compared to the other groups (p< 0.001). The median iAUC for the remaining groups were as follows: pure water 2885.1 (2405.7–3005.3), alcohol antidote 2973.9 (2744.2–3369.5), Proanecy Hepa without Silymarin 2295.9 (1222.5–2569.4), Silymarin 3411.8 (3006.2–3922), and Liver support milk 2739.4 (2431.8–3149.4). Furthermore, individuals who consumed 6ml/kg of Proanecy Hepa before alcohol intake maintained BAC below the positive threshold of 10 mg/dl at all measured time points (60, 120, 180, and 240 minutes). In contrast, individuals in the control groups exceeded the positive threshold at those time points except for minute 240.

Conclusions: The study suggests that consuming 6 ml/kg of Proanecy Hepa milk 30 minutes before consuming 0.5g of ethanol/kg can help prevent blood alcohol levels from exceeding the positive threshold of 10 mg/dl.

Keywords: *Proanecy Hepa milk, alcohol antidote, blood alcohol concentration, liver support milk, Silymarin.*

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I. INTRODUCTION

Alcohol consumption has led to health and social issues [1]. In 2010, the average daily alcohol intake per person over 15 years old was 13.5 grams [2]. Vietnam saw an increase in average alcoholic beverage consumption from 3.8 to 6.6 liters of ethanol per person per year [2]. Excessive blood alcohol levels impair decision-making, motor control, and judgment, leading to reduced abilities and unsafe behavior, especially in traffic. Alcohol-related deaths account for 21.8% of traffic accidents [3]. Decree 100/2019/ND-CP enforces penalties for individuals with blood alcohol concentration (BAC) exceeding a certain level [4].

Alcohol is rapidly absorbed into the bloodstream (20% in the stomach, 80% in the small intestine), and consuming alcohol on a full stomach slows down absorption, particularly with high-protein meals [5]. Research has shown that branched-chain amino acids (BCAAs) can prevent fat accumulation and mitochondrial dysfunction caused by alcohol consumption in rodents [6]. Proanecy Hepa, a high-protein milk, contains 35.2g protein in 100g milk. Moreover, with 19g BCAAs in 100g milk can Proanecy Hepa affect the absorption of alcohol into the bloodstream? So the study aimed to determine if consuming 6 ml/kg of Proanecy Hepa milk, 30 minutes before drinking alcohol, could limit the increase in BAC in individuals who consumed 0.5g of alcohol/kg.

II. METHODS

2.1. Study design

A self-controlled clinical trial was conducted, involving 10 healthy subjects who had fasted for a minimum of 10 hours overnight. The trial consisted of six ethanol pharmacokinetic crossover trials, following the protocol established by Mitchell MC Jr et al. [7]. The study received approval from the Ethics Committee in Biomedical Research of Military Hospital 7A, as per Decision No. 26/HD-ĐNCYSH dated April 21, 2022. Furthermore, the study proceeded only after obtaining written consent from all participants.

2.2. Research process

The experiment spanned six weeks, with each week focusing on a different test or reference substance. During the first week, we examined the reference substance, which was pure water given at a dosage of 6 ml/kg. In the second week, the participants received the first test substance, which consisted of two tablets of an alcohol antidote along with a drink containing purified water at a dosage of 6 ml/kg. In the third week, the participants consumed Proanecy Hepa milk at a dosage of 6 ml/kg. In the fourth week, the participants consumed Proanecy Hepa milk without Silymarin at the same dosage. In fifth week, participants took Silymarin orally at a dosage of 50 mg/kg, along with 6 ml/kg of purified water. Finally, in the sixth week, the participants consumed liver support milk at a dosage of 6 ml/kg, 30 minutes before the experiment. On the

day before each experiment, the participants were instructed to avoid consuming legumes, sweet fruits, alcoholic drinks, and fermented juices, and to refrain from heavy exercise. They were allowed to drink only boiled water. On the day of the experiment, the participants arrived at the hospital at 6 a.m and rested for 15 minutes. An intravenous cannula was inserted, and a baseline BAC sample (t_0) was taken. After the initial blood sample, the participants consumed the reference or test substance within 15 minutes. Thirty minutes later, the participants drank 0.5g ethanol/kg or 9.4 ml/kg of 5.3% "333" beer, 50% every 10 minutes, total beer drinking time was 20 minutes. Additional blood samples (t_1, t_2, t_3, t_4) were collected at 60, 120, 180, and 240 minutes after drinking the beer. If any participants exhibited symptoms of acute alcohol poisoning, such as fatigue, slurred speech, or confusion, or if their BAC exceeded 100 mg/dl, the trial would be immediately stopped. The participant would then be transferred to the hospital emergency department and would be withdrawn from the study.

2.3. Research substances

Table 1. *Nutritional composition of liver support milk and Proanecy Hepa milk/100g*

Nutrition	Unit	Liver support milk	Proanecy Hepa milk
Energy	kcal	444.0	473.0
The protein	g	18.0	35.2
Branched amino acid (BCAA) [1]	g	3.0	19.0
Amino Acid Score [2]	-	-	400.1
Carbohydrates available	g	61.0	47.7
Fiber (FOS: Fructose Oligo Saccharide)	g	3.2	4.2
Fat	g	15.1	21.2
Transfat	g	-	0.0
Mono Unsaturated Fatty Acid	g	4.1	0.1
Poly Unsaturated Fatty Acid	g	1.1	0.04
Saturation Fatty Acid	g	-	14.0
Cholesterol	mg	-	16.7
MCT (Medium Chain Triglyceride)	g	4.2	15.6
Fatty acids have 6 to 10 carbons	g	-	16.5
Fatty acids have 10 to 12 carbons	g	-	0.8
Fatty acids have more than 12 carbons	g	-	1.3
Inflammation index (IF) [3]		-	69.2

[1] *Branched Amino Acid (BCAA: Branch Chain Amino Acid) : Valin, leucin, Isoleucin*

[2] *Amino acid score > 100 ⇒ high biological value protein*

[3] *IF = Total (nutrient/day × inflammatory coefficient for each nutrient).*

The anti-inflammatory index is classified as a strong anti-inflammatory (≥ 200), moderate anti-inflammatory (101–200), mild anti-inflammatory (1–100), mild inflammation (-1 to -100), moderately inflammatory (-101 to -200), and strong inflammation (≤ - 201).

2.3.1. Substance types

Reference was pure water 6ml/kg.

Test substances included**:** (i) Alcohol antidote, each tablet contains 50mg N-Acetylcysteine, 15mg vitamin B_6, 4×10^9 CFU *Bacillus subtilis*. Dose 2 tablets, and drink with 6 ml/kg of purified water; (ii) Proanecy Hepa milk, 6 ml/kg; (iii) Proanecy Hepa milk without Silymarin, 6ml/kg; (iv) Silymarin 50 mg/kg orally with 6 ml/kg of purified water; and (v) Liver support milk, 6 ml/kg.

2.3.2. Test substance ingredients

Liver support milk consists of a mixture of milk powder, whey protein, soy protein, dietary fiber (FOS), medium chain triglyceride (MCT oil), powdered sugar, vitamin-mineral mixture, choline, and colostrum. The nutrient contents of liver support milk are shown in Table 1.

Proanecy Hepa milk (Table 1) consists of a blend of whey protein isolate, dietary fiber (FOS), medium chain triglycerides (MCT oil), powdered sugar, instant coffee, silymarin, vitamin-mineral blend, L-carnitine, and probiotics. Proanecy Hepa is a product of ANNECY HEALTHCARE company, which complies with the food hygiene criteria specified in Circular No. 43/2014/TT-BYT issued on November 22, 2014.

"333"Beer has an ethanol concentration of 5.3% v/v, and 9.4 ml beer has 0.5g ethanol.

2.4. Research subjects

2.4.1. Selection criteria

10 healthy students, aged 20–25 from Ho Chi Minh City University of Technology were selected for the study with the following criteria:

- Not malnourished or obese (BMI 18.5–22.9 kg/m^2);
- No hypertension (blood pressure < 130/90 mmHg);
- No allergy to cow's milk, soy milk, or beer;
- Not addicted to alcohol;
- Voluntarily agreed to participate in the study and signed a commitment to participate in all 6 trials.

2.4.2. Exclusive criteria

A student was excluded from the study when having one of the following criteria:

- A serious illness or surgery requiring hospitalization 3 months before the procedure;
- Chronic diseases such as diabetes, liver failure, kidney failure, and heart failure;
- Diseases affecting absorption such as gastritis, colitis, irritable bowel syndrome, etc;
- Taking drugs that affect the absorption and metabolism of ethanol such as aspirin, naloxone, acetylcysteine, fomepizole, vitamin B_1, and activated charcoal;
- Did not participate in all 6 trials;
- BMI< 18.5 kg/m^2 or BMI≥ 23 kg/m^2;
- During the trial, if the subject showed signs of acute alcohol intoxication [8] such as fatigue, severely impaired judgment, impaired coordination, slurred speech, confusion, and blood ethanol ≥100mg/dl, discontinue the trial and be transferred to the hospital emergency department.

2.5. Sample size and sampling technique

A total of 20 students who had enrolled were invited to participate in the study. The selection was carried out based on their medical examination records, interviews, weight measurements (to calculate BMI), blood pressure readings, and their willingness to volunteer and commit to the entire trial process for a total of 6 sessions. After the selection process, 10 students were deemed suitable and included in the study. This sample size falls within the recommended range of 9-15 for pharmacokinetic studies [9].

2.6. Variables and data collection

Blood ethanol was measured by enzyme method using alcohol dehydrogenase, wavelength 340 nm, Cobas C501, Roche. The positive threshold of blood ethanol is 10 mg/dl.

The ability to increase blood ethanol (EI: Ethanol Index) with the dose of food intake was calculated according to the formula:

$$EI_{\,test\ substance} = \frac{iAUC_{test\ susbtance}}{iAUC_{reference\ susbtance}} \times 100$$

iAUC (Area Under Curve) is the area under the curve of the curve showing the blood ethanol concentration at the time points 0 (t_0), 60 (t_1), 120 (t_2), 180 (t_3), 240 minutes (t_4). AUC= $\sum_{n}^{x=1} A_X$. iAUC of the rise in blood ethanol was calculated following ISO 26642:2010 [10].

2.7. Statistical analysis

Data are presented as mean±SME (standard error of the mean). The mean within-subject CV for the reference or test substances for the group of subjects tested must be ≤30 %. If the mean CV is greater than 30 %, one outlying result for the reference test in each subject can be deleted. iAUC of blood ethanol are presented as median (interquartile range).

The difference in Ethanol Index, iAUC of blood ethanol in response to a loading dose of 6 studied substances was determined by Post hoc test following One-way ANOVA. The difference was statistically significant when $p<0.05$.

III. RESULTS

3.1. Research sample characteristics

The study enrolled a total of 10 participants, 5 men and 5 women. The participants had a mean age of 21.0±0.1 years and an average BMI of 21.4±0.3 kg/m^2. At t_0 (after a 10-hour fasting period), the group receiving the Silymarin loading dose exhibited a significantly higher blood ethanol level (1.042±0.302 mg/dl) compared to the pure water group (0.186±0.074 mg/dl), alcohol antidote group (0.028±0.005 mg/dl), Proanecy Hepa group (0.072±0.039 mg/dl), Proanecy Hepa-no Silymarin group (0.156±0.075 mg/dl), and liver support milk group (0.002±0.000 mg/dl). This difference was statistically significant (p <0.000).

3.2. The change in blood ethanol concentration

Throughout the experiment, the BAC reached its peak at 60 minutes and gradually decreased, falling below the positive threshold after 240 minutes. Remarkably, the Proanecy Hepa group exhibited the lowest peak BAC, measuring 5.5±2.2 mg/dl, which remained below the positive threshold. In contrast, the group that consumed Silymarin had the highest concentration at 44.3±3.5 mg/dl.

Additionally, the three groups that consumed various forms of milk (Proanecy Hepa, Proanecy Hepa without Silymarin, and liver support milk) displayed lower blood alcohol levels compared to the three groups that did not consume milk (pure water, alcohol antidote, and Silymarin). The BACs were measured as 5.5±2.2 mg/dl, 22.5±2.9 mg/dl, and 29.6±3.5 mg/dl, respectively, for the milk-consuming groups, while the non-milk-consuming groups showed concentrations of 35.9±2.0 mg/dl, 38.1±5.0 mg/dl, and 44.3±3.5 mg/dl, respectively. These differences in BAC between the Proanecy Hepa group and the other five groups were statistically significant at time points t_1, t_2, and t_3 (p<0.000) according to Figure 1

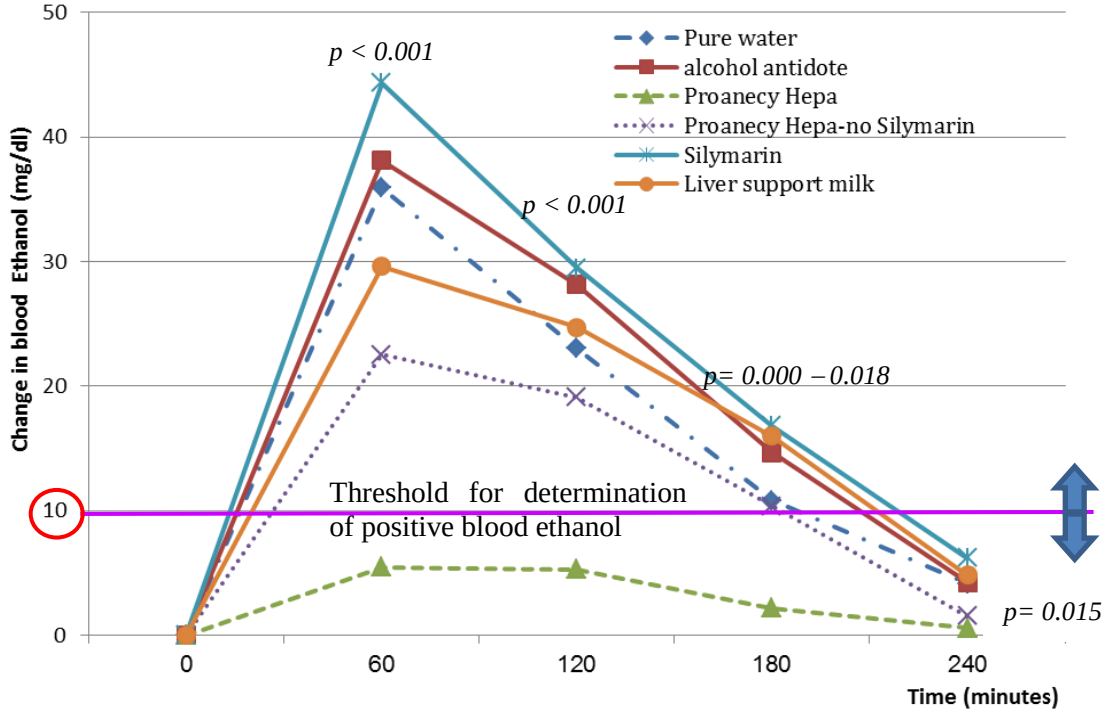

Figure 1. *Changes in blood ethanol levels at baseline and after drinking products.*

3.3. Increase in blood ethanol concentration expressed as area under the curve

3.3.1. iAUC the reference substance "pure water"

The iAUC (incremental area under the curve) for the reference substance, "pure water," was calculated to be 2885.1 (2405.7; 3005.3). The coefficient of variation (CV) for this measurement was determined to be 8.9%, which was below the threshold of 30%. Therefore, no variables were identified as outliers, and there was no need to eliminate any data points (as shown in Table 2).

3.3.2. iAUC test substances

The area under the curve (iAUC) values were calculated for the test substances consumed by 10 individuals, including the alcohol antidote, Proanecy Hepa milk, Proanecy Hepa without Silymarin milk, Silymarin, and Liver support milk. These iAUC values had a coefficient of variation (CV) below 30% as indicated in Table 2, allowing for the calculation of EI (Ethanol index). The median iAUC for the alcohol antidote was 2973.9 (2744.2–3369.5). For Proanecy Hepa milk, it resulted in 170.9 (50.5–470.8). The median iAUC for Proanecy Hepa without Silymarin was 2295.9 (1222.5–2569.4). Silymarin had a median iAUC of 3411.8 (3006.2–3922.0), and liver support milk exhibited a median iAUC of 2739.4 (2431.8–3149.4) (as shown in Table 2)

Table 2. *The increase in blood alcohol concentration was expressed as iAUC and ethanol index using "pure water" as the reference substance.*

Test products	Area of incremental under curve		Ethanol index	
	Median (interquartile)	CV (%)	Average±SME	CV (%)
Pure water	2885.1 (2405.7–3005.3)	8.9	100	
Alcohol Antidote	2973.9 (2744.2–3369.5)	12.4	120.9±17.4^{cd}	14.4
Proanecy Hepa milk	170.9 (50.5–470.8)	29.7	18.9±5.7^{a}	29.9
Proanecy Hepa-no Silymarin milk	2295.9 (1222.5–2569.4)	13.3	70.4±7.0^{b}	9.9
Silymarin	3411.8 (3006.2–3922.0)	10.4	139.9±17.1^{d}	12.2
Liver support milk	2739.4 (2431.8–3149.4)	10.8	96.9±8.2^{bc}	8.5

SEM: Standard error of the mean; CV: Coefficient of Variation, iAUC: *Area of incremental under curve.*

The difference in data between trials was analyzed by post-hoc test following one-way ANOVA and expressed as the difference of letters a,b,c, and d on the data, with $p<0.001$.

3.3.3. An increase in blood ethanol concentration of test substances

EI value was calculated from the iAUC of the test food and reference food according to the formula:

$$\text{EI}_{\text{test substance}} = \frac{\text{iAUC}_{\text{test substance}}}{\text{iAUC}_{\text{reference substance}}} \times 100$$

The EI of pure water (substance reference) had defaulted to 100. EI of alcohol antidote was 120.9±17.4 with CV 14.4%, Proanecy Hepa was 18.9±5.7 with CV 29.9%; Proanecy Hepa-no Silymarin was 70.4±7.0 with CV 9.9%, Silymarin was 139.9±17.1 with CV 12.2% and Liver support Milk was 96.9±8.2 with CV 8,5% (Table 2). The EI of Proanecy Hepa was only 1/4 to 1/6 of the EI of the remaining 4 test substances, the difference was statistically significant with $p < 0.000$ (Table 2).

IV. DISCUSSION

Proanecy Hepa is an enhanced dairy product that contains probiotics, Silymarin, minerals, vitamins, micronutrients, significant levels of protein, and branched-chain amino acids (BCAAs). The findings from the study indicate that Proanecy Hepa effectively reduced alcohol absorption by a mere 19%, as measured by the *EI (Ethanol Index)* when compared to the water group. Moreover, it demonstrated a reduced alcohol absorption rate of only 16% when compared to the antidote group (representing the impact of probiotics on alcohol elimination). When compared to the group consuming milk specifically designed to support liver function (containing BCAAs), the Proanecy Hepa group exhibited a modest alcohol absorption rate of just 20%. Furthermore, when comparing the Proanecy Hepa group to the Silymarin group or the group consuming Proanecy Hepa without Silymarin, the alcohol absorption rates were merely 14% and 27% respectively.

The concentration of alcohol in the blood is influenced by various factors, including (i) the amount consumed, (ii) the presence of food in the stomach, (iii) gastric emptying rate, and (iv) alcohol oxidation. Only 10% of ethanol is excreted through breath, sweat, and urine, while 90% is eliminated through liver oxidation [11]. This study showed that when loading Proanecy Hepa 30 minutes before consuming ethanol, blood ethanol concentration remained below the positive threshold at different time intervals, indicating that Proanecy Hepa affects factors number 2 to 4. Alcohol absorption is faster in the duodenum and jejunum compared to the stomach, and the rate of gastric emptying plays a crucial role in alcohol absorption [12]. Ingested alcohol can also be oxidized in the stomach by specific enzymes, σADH (σAlcohol Dehydrogenase) and type I and III ADH, leading to the formation of acetate, which is then excreted, so reducing its entry into the bloodstream [13] The presence of food in the stomach slows down gastric emptying and reduces alcohol absorption. Research has shown that a meal rich in fat, carbohydrates, or protein delays gastric emptying [14], supporting the findings of the study where 3 types of milk which were liver support milk (EI=96.9±8.2), Proanecy Hepa-no Silymarin milk (EI=70.4±7.0), Proanecy Hepa milk (EI=18.9±5.7) resulted in lower ethanol absorption, compared to pure water (EI=100), alcohol antidote (EI=120.9±17,4), and Silymarin (EI=139.9±17). However, even though it's also milk, the EI of the loading dose of Proanecy Hepa was only 1/5 of that of liver support milk (18.9±5.7 *vs.* 96.9±8.2, p=0.001). The protein content of Proanecy Hepa, which is twice that of liver-support milk, may contribute to the slower absorption of ethanol [5].

Ninety percent of ethanol is eliminated from the body through oxidation in the liver [11]. The liver plays a major role in alcohol metabolism, with liver Alcohol Dehydrogenase (ADH) being the primary enzyme system involved. NAD serves as a cofactor in this process, resulting in the production of acetaldehyde and NADH. Acetate is further converted to CO_2, fatty acids, ketone bodies, cholesterol, and steroids. Cytochrome P450, specifically CYP2E1, is an alternate pathway for

alcohol elimination, particularly at high ethanol consumption [11]. Silymarin, derived from milk thistle, has been found to inhibit cytochrome P4502E1 induction, promoting ethanol metabolism in the liver [15]. The study confirmed that Silymarin plays a role in preventing an increase in blood ethanol concentration when comparing Proanecy Hepa with and without Silymarin with the EI of the trial with a loading dose of Proanecy Hepa only 1/4 compared with Proanecy Hepa-no Silymarin (18.9±5.7 *vs.* 70.4±7.0, p=0.01).

Research has shown that binding *Bacillus subtilis* with alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) enzymes accelerates alcohol detoxification in mice [16]. A clinical trial on humans using a mixture of Lactobacillus and Bifidobacterium demonstrated a significant reduction in blood alcohol and acetaldehyde levels [17]. In the study, Proanecy Hepa, milk supplemented with probiotics, showed better effects on ethanol concentration compared to an alcohol antidote containing Bacillus subtilis, highlighting the benefits of combining milk and probiotics in alcohol detoxification. Thus, the combination of milk and probiotics is better than probiotics alone in alcohol detoxification, and nutrients in milk may contribute to this effect as explained by the Wissel study [18] as the metabolism of alcohol in the stomach satiety than in the fasted state because of higher ADH concentrations and increased transport of equivalent reducing agents into the mitochondria while increasing blood flow to the liver. In addition to Silymarin and probiotics, fructose enhances alcohol metabolism by facilitating the conversion of NADH to NAD+ and promoting mitochondrial oxygen uptake [17]. The presence of high-level Fructose Oligo Saccharide (FOS) in Proanecy Hepa may contribute to increased alcohol oxidation in the liver, leading to faster elimination of ethanol from the body.

V. CONCLUSION

Consuming Proanecy Hepa milk at a dosage of 6 ml/kg 30 minutes before drinking 0.5g of ethanol/kg has been shown to prevent blood ethanol levels from exceeding the positive blood ethanol threshold of 10 mg/dl. However, further research is necessary to better understand the underlying mechanisms responsible for these effects and to optimize Proanecy Hepa's efficacy in mitigating symptoms of intoxication.

It is important to note that the study did not directly investigate the correlation between levels of intoxication and BAC. Regardless of BAC levels, if an individual displays signs of intoxication, it is unsafe for them to participate in activities such as driving. Additionally, the study primarily focused on measuring BAC and did not assess the concentration of alcohol in exhaled breath. As a result, it is unlikely that the alcohol concentration in breath would fall below the legal threshold.

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