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ORIGINAL ARTICLE

Sublingual caffeine delivery via oral spray does not accelerate blood caffeine increase compared to ingestion of caffeinated beverages

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Abstract

Introduction Buccal absorption of caffeine bypasses digestion, can elicit peak serum caffeine concentration within ~ 30 min of administration, and thereby may elicit cognitive benefits faster than ingesting caffeine. Caffeine mouth sprays are commercial products that involve sublingual delivery, but their ability to increase blood caffeine is unexamined.

Purpose This study tested whether blood caffeine would be increased and reach peak concentrations sooner after using mouth spray compared to ingesting coffee or an energy drink.

Methods Fourteen adults (6 males, 8 females; 24 ± 3 years, 69.9 ± 9.3 kg) abstained from caffeine for 16 h, ate a standardized breakfast, then consumed 60 mg of caffeine via either mouth spray, coffee, or energy drink in a randomized, crossover manner. In the following 90 min, serum caffeine was determined throughout, and cognitive function was assessed at ~ 30 and ~ 90 min.

Results Serum caffeine was increased compared to baseline in all conditions ($p < 0.0001$) but was not different at any timepoint between the mouth spray, coffee, and energy drink ($p = 0.06$). Caffeine area under the curve was not different after mouth spray, coffee, or energy drink (61 [54–73], 82 [51–119], 68 [43–78] min*mg/L respectively, $p = 0.22$) nor was peak concentration (1.6 [1.2–1.8], 1.9 [1.4–2.4], 1.2 [0.8–3.0] mg/L respectively, $p = 0.19$). Within the mouth-spray condition, serum caffeine was higher than baseline from 10 to 90 min ($p < 0.03$) but not at 5 min ($p = 0.50$), and peak concentration occurred 90-min after use. Performance on cognitive tests was unaffected by caffeine type ($p > 0.22$).

Conclusion Sublingual administration of caffeine via mouth spray did not increase serum caffeine concentration faster than ingesting caffeinated beverages.

Keywords Hemodynamics · Pharmacokinetics · Pharmacodynamics · Blood pressure · Stroop · Digit Symbol Substitution Task (DSST)

Introduction

Caffeine is a socially acceptable and widely used drug, most commonly recognized for its role as a central nervous system stimulant and the associated cognitive and physical benefits (Cappelletti et al. 2015; Davis et al. 2003). Acutely increasing blood caffeine concentration can improve cognitive functioning (e.g., mood, memory, perceptions of fatigue, alertness, concentration, etc.) (McLellan et al. 2016), alter resting physiologic processes (e.g., blood pressure regulation, cerebral blood flow) (Hartley et al. 2004), improve exercise performance (Guest et al. 2021), and alter sleep parameters (Antonio et al. 2024). The effects of caffeine use on cognition and endurance performance are well-researched; however, as noted in a recent review, there are several questions that remain unanswered including effects of doses < 3 mg/kg

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body mass, the time-course of such responses, comparisons between different caffeine types, and efficacy of novel forms of delivery (Tallis et al. 2022). Thus, to advance the field, research should test nuanced considerations surrounding the known efficacy of caffeine.

Current recommendations on the use of caffeine as an ergogenic aid suggest ingesting ~ 3–6 mg/kg body mass ~ 1 h before an event to enhance performance as this timing coincides with peak blood caffeine (Guest et al. 2021). However, there may be certain situations in which needing to wait ~ 1 h for caffeine to elicit its beneficial effects is not practical/desirable or the ingestion of caffeine elicits gastrointestinal discomfort, and some evidence suggests that doses < 3 mg/kg body mass may also be ergogenic (Spriet 2014). Alternative forms of caffeine that do not require ingestion are gaining interest, including caffeinated gums, caffeine mouth rinsing, and caffeinated nasal sprays (Wickham & Spriet 2018, Tallis et al. 2022). Of non-ingestible caffeine types, caffeine gum has the strongest supporting evidence, and a recent meta-analysis concluded that chewing caffeine gum can improve exercise performance if used ~ 15 min before the test (Barreto et al. 2023). This potentially faster onset of an ergogenic effect compared to ingested caffeine could relate to the absorption of caffeine from chewing gum occurring through the buccal mucosa of the oral cavity which bypasses digestive processes. Indeed, the initial increase of blood caffeine as well as the peak caffeine concentration occurred sooner (~ 20–30 vs. 60–90 min) after chewing caffeinated gum compared to ingestion of caffeine containing capsules (Kamimori et al. 2002). Thus, buccal absorption is a viable mechanism to quickly increase blood and elicit the associated benefits.

Like buccal absorption, sublingual drug absorption bypasses digestion and is a well-established drug delivery method that may be more effective due to a higher capillary density (Hua et al. 2019). Caffeinated mouth sprays are an emerging product, which allows for direct sublingual administration of a known dose of caffeine. Currently, no data exist regarding the efficacy of caffeinated mouth sprays to increase blood caffeine concentration, but this method of administration may elicit similar responses to caffeinated chewing gums as both bypass digestion. Thus, sublingual caffeine administration via mouth spray may result in a faster blood caffeine increase than ingested caffeine sources, similar to how chewing gum was reported faster than capsules (Kamimori et al. 2002). A comparison to caffeine capsules may however be practically limited as the vast majority of individuals ingest caffeine from beverages, e.g., coffee, energy drinks. As such, the most ecologically valid comparison of a novel caffeine administration method would be to compare it to caffeinated beverages.

The purpose of this study was to determine whether sublingual caffeine administration via a novel mouth spray results in faster increases in blood caffeine concentration compared to traditional caffeinated beverage ingestion. The time-course increase of blood caffeine concentration and improved cognitive performance was assessed in habitual caffeine users following consumption of 60 mg of caffeine via either a mouth spray applied sublingually or ingestion of coffee or energy drink. We hypothesized that the onset and peak of increased blood caffeine concentration would occur sooner after using mouth spray compared to ingesting coffee or an energy drink.

Methods

Participants

Fourteen young adults (6 males, 8 females; 24 ± 3 years, 69.9 ± 9.3 kg, 170 ± 6 cm) who habitually consumed caffeine were recruited for the study and no dropouts occurred. Inclusion criteria were 18 to 50 years of age and consuming at least one serving of caffeine per day at least 6 days per week. Participants were recruited from the University of Guelph campus via poster advertisements. Written informed consent was obtained from all participants and the project was approved by the University of Guelph Research Ethics Board (REB#23-11-034). An a priori sample size estimation determined that $n = 12$ were required to detect a large effect size ($f = 0.40$, corr among rep measures = 0.5) at $a = 0.05$ with 80% power using a repeated-measures analysis of variance (1 group, 3 measurements, epsilon = 1). A large effect size for blood caffeine 30 min after caffeine administration was estimated from a study that compared blood caffeine after chewing administration of caffeine gum and capsules (Kamimori et al. 2002). To preserve power, $n = 14$ participants were recruited.

Study design

This randomized, crossover, open-label study involved one screening visit, familiarization of the cognitive test battery, and three experimental trials. The experimental trials were identical with the exception of the method of caffeine consumption, i.e., ingestion of coffee, ingestion of energy drink, or sublingual administration of mouth spray. Each participant was randomized into one of two treatment orders using a random number generator (randomizer.org) in block sizes of six, six, and two. The primary outcome measurement was blood caffeine. Secondary measures included heart rate, blood pressure, and performance on the digit symbol substitution task and Stroop test. Data were analyzed blind to condition. The study methods were registered in Open Science Framework (osf.io/m9t3v).

Experimental trials

Data were collected in the Human Performance and Health Research Lab at the University of Guelph. All three experimental trials were completed within ~ 14 days and occurred at the same time of day within 1 h for each participant. Participants arrived at the lab in the morning after an overnight fast from food (fasting duration consistent within a participant) and having abstained from consuming caffeine for at least 16 h. After verbal confirmation of these standardizations, an indwelling venous catheter was inserted into an antecubital vein.

The experimental protocol included baseline assessments, a meal, caffeine intake, and a 90-min evaluation period (Fig. 1). Baseline measurements involved a cognitive testing battery, venous blood sampling, and determination of heart rate and blood pressure as the average of six consecutive oscillimetric measurements (BPTru Medical Devices, Coquitlam, Canada). The standardized meal contained 2%-milk-fat Greek yoghurt and oatmeal prepared with milk (255 kcal). After breakfast, 60 mg of caffeine was administered via either (1) coffee ingestion, (2) energy drink ingestion, or (3) mouth-spray administration as per the randomized, crossover allocation described above. The energy drink was commercially available (Red Bull, sugar free). Coffee was prepared as espresso (~ 60 mg caffeine per 30-ml fluid) using an automated machine and coffee pods (Nespresso) that had been evaluated by a third party for caffeine content (Desbrow et al. 2019). Warm water was added to the espresso such that total volume of coffee was equal to the volume of the energy drink (190 mL). Coffee pods were obtained from the same order and lot numbers were matched within a participant block. The caffeinated mouth spray (167-mg caffeine per mL) was preceded by drinking 190 mL of water and then administered per manufacturer instructions, i.e., three sprays (20 mg caffeine per spray) each under the tongue and held for ~ 2 min before swallowing. Participants remained seated for the 90 min following caffeine consumption; venous blood was sampled at 5, 10, 20, 30, 45, 60, and 90 min, heart rate and blood pressure at 30–35 and 80–85 min, and cognitive test battery at 25–30 and 85–90 min.

The cognitive test battery involved the digit symbol substitution task (DSST) (Thorndike 1919) and the Stroop test (Stroop 1935). Tests were completed on a laptop computer (Inquisit version 6, millisecond, Seattle, USA) and required the participant to press computer keys in response to various stimuli. The digital symbol substitution task first linked nine symbols with numbers 1 through 9, then the participant was shown a number from 1 to 9 and required to input the correct linked symbol. Participants were instructed to answer as many questions as possible correctly within the set duration. The Stroop test briefly flashed a word that is a color and written in a color, e.g., the word "green" may be written in blue text. Participants were required to indicate the color of the word not the word itself. Participants were instructed to complete all 84 questions as accurately and quickly as possible.

Serum caffeine analysis

Venous blood was collected in silicon-coated vacutainers, left at room temperature for 30 min to clot, centrifuged (10 min, 4°, 3600 rpm), and the serum aliquot promptly stored at -80 °C. Concentration of caffeine in serum samples represents the average of duplicate values determined using a commercial enzyme linked immunosorbent assay (ELISA) as per manufacturer instructions (catalog number DEIA6842; Creative Diagnostics, New York, USA). Enzyme-linked immunosorbent assay quantification of serum caffeine concentration was validated against the gold standard method and has been used to determine blood [caffeine] previously (Ohmichi et al. 2020; Matsumura et al. 2023).

Statistics

Data were assessed for normality and lognormality via Sharipo-Wilks test. Absolute serum caffeine concentration and the increase in serum caffeine concentration at a given timepoint subtract baseline were lognormal and therefore log transformed before statistical analysis. Serum caffeine concentration, cognitive test outcomes, and hemodynamic variables were tested for differences by within-subject mixed-effects analysis (condition * time). Serum caffeine concentration within the caffeine spray condition only, peak serum caffeine concentration, and area under the curve were compared using within-subject mixed-effects analysis (time). Significant *F*-tests were followed by post-hoc Tukey's tests. Significance

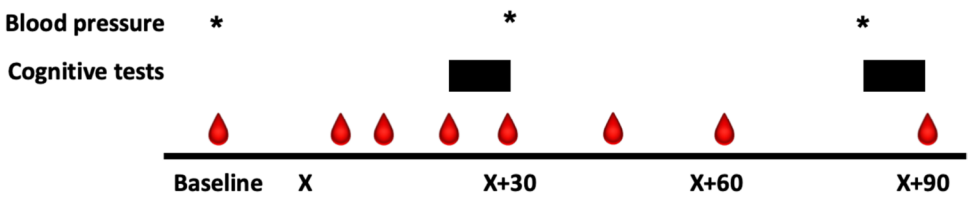

Fig. 1 Schematic overview of the experimental trial protocol

was accepted at $p < 0.05$. Normal data are reported as mean ± standard deviation, non-normal data as median [interquartile range], change scores as mean [95% confidence intervals], and effect size for mixed-effects analysis as F and pairwise comparisons as Cohen's d_z.

Results

Serum caffeine concentration was higher at 10, 30, and 90 min compared to baseline (time $p < 0.0001$ and $F = 46.4$, condition $p = 0.06$ and $F = 3.2$, interaction $p = 0.08$ and $F = 2.2$) (Fig. 2A). Within the caffeine spray condition, serum caffeine concentration (time $p < 0.0001$ and $F = 30.7$), was higher from 10 min through 90-min post-administration compared to baseline ($p < 0.03$ and $d_z > 1.2$ for all) but not different between 5-min post-administration vs. baseline ($p = 0.50$, $d_z = 0.49$) (Fig. 2B). Peak serum caffeine concentration occurred at 90-min post administration of mouth spray in all but one participant. The increase in serum caffeine concentration from baseline was unaffected by condition ($p = 0.14$ and $F = 2.3$) or condition*time ($p = 0.04$ and $F = 3.3$, post-hoc $p > 0.10$). Neither area under the serum caffeine concentration by time curve nor peak serum caffeine concentration were affected by condition (Table 1).

Neither the number of correct responses relative to total responses nor total correct responses on the DSST was affected by time, condition or time*condition ($p > 0.22$ for all) (Fig. 3A). Compared to baseline, the total number of correct responses per DSST was 4[1–7] responses higher at 90 min vs. baseline and 1[1–4] responses lower at 30 min vs. baseline. The total number of correct responses per DSST at baseline had a coefficient of variation of 7.7 ± 4.3% or 6 responses. The number of correct responses per Stroop test over all conditions and timepoints was 81 ± 3 of 84 total questions (condition $p = 0.82$, time, $p = 0.09$, time*condition $p = 0.93$). Average response latency per Stroop test (Time $p < 0.0001$) was different at all timepoints (baseline = 667 ± 81 ms, 30 min = 710 ± 89 ms, 90 min = 770 ± 154 ms, $p < 0.02$ for all), but was unaffected by condition ($p = 0.83$) or time*condition ($p = 0.27$) (Fig. 3B). Compared to baseline, the average response latency per Stroop test was 61[34–155] ms faster at 30 min vs. baseline and 102[71–134] ms faster at 90 min vs. baseline. Average response latency per Stroop at baseline had a coefficient of variation of 13.6% or 111 ms.

Systolic blood pressure (time $p = 0.002$) was higher at 60 and 90 min vs. baseline (baseline: 102 ± 7, 30-min: 106 ± 7; 90-min: 105 ± 8 mmHg, $p < 0.03$ for both), but was unaffected by condition ($p = 0.20$) or time*condition ($p = 0.60$). Diastolic blood pressure was 69 ± 7 mmHg at baseline, 69 ± 6 mmHg at 30 min, and 71 ± 7 mmHg at 90 min (time $p = 0.08$, condition $p = 0.32$, time*condition $p = 0.92$). Heart rate was 65 ± 10 beats/min at baseline, 65 ± 9 beats/min at 30 min, and 64 ± 9 beats/min (time $p = 0.82$, condition $p = 0.21$, time*condition $p = 0.60$).

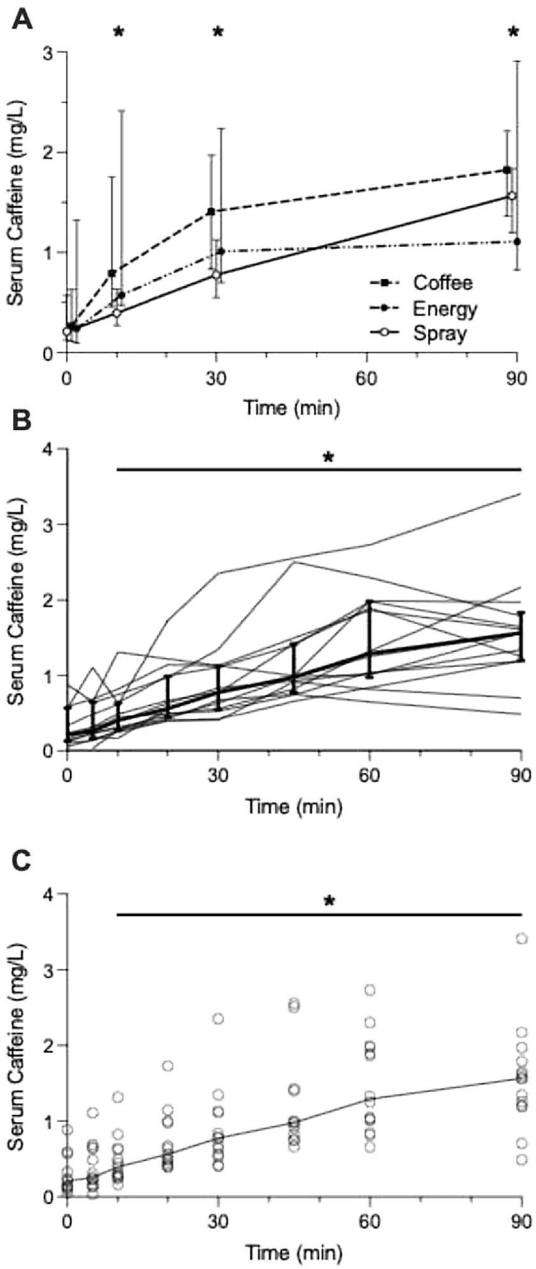

Fig. 2 **A** Serum caffeine concentration after sublingual administration of caffeine mouth spray or ingestion of coffee or energy drink and (**B** and **C**) individual blood caffeine responses to the caffeine mouth spray. Data points with error bars represent median and interquartile range ($n = 14$ for spray and coffee conditions, $n = 10$ for energy), dots in panel B represent individual points, and lines without error bars in panel B connect individual participant data. *$p < 0.05$ vs. baseline (Tukey's test) after a significant main effect of time from a repeated-measures mixed-effects analysis (condition*time) on log transformed serum caffeine data

Table 1 Serum caffeine concentration characteristics in the 90 min following consumption of 60 mg of caffeine via oral spray, coffee, and commercial energy drink

	Spray	Coffee	Energy	*P*	*F*
Peak concentration (mg/L)	1.6 [1.2–1.8]	1.9 [1.4–2.4]	1.2 [0.8–3.0]	0.19	1.8
Area under curve (min*mg/L)	61 [54–73]	82 [51–119]	68 [43–78]	0.22	1.6

Data are median [interquartile range] ($n = 14$ for spray and coffee conditions, $n = 10$ for energy)

*$p < 0.05$ vs. Spray (post-hoc Tukey's test) following mixed-effects analysis (spray vs. coffee vs. energy) on log transformed data. p value and effect size F are from mixed-effect analysis

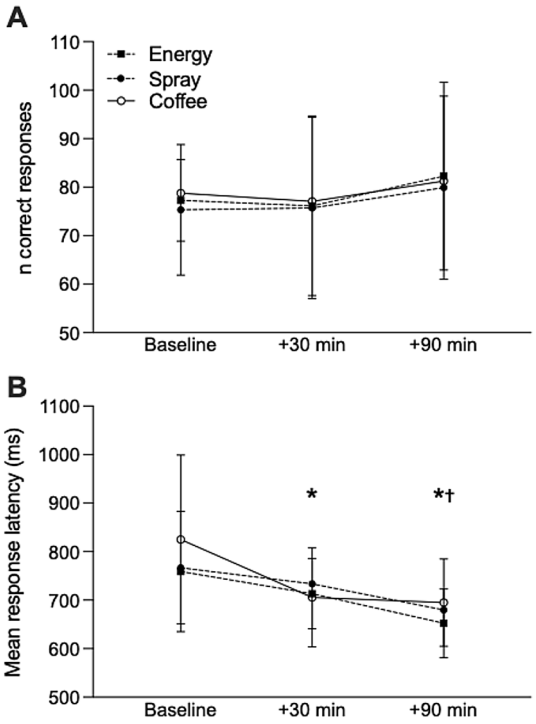

Fig. 3 Cognitive performance on the digit symbol substitution task (**A**) and Stroop test (**B**) after sublingual administration of caffeine mouth spray or ingestion of coffee or energy drink. Data points with error bars represent means and standard deviation ($n = 14$ for spray and coffee conditions, $n = 10$ for energy). *post-hoc Tukey's test $p < 0.05$ vs. baseline and †$p < 0.05$ vs. + 30 min after main effect of time ($p < 0.05$) from repeated-measures mixed-effects analysis

Discussion

The primary observation of this study was that the sublingual administration of caffeine via mouth spray did not speed the increase of serum caffeine concentration nor reduce the time-to-peak serum caffeine concentration compared to ingestion of caffeinated beverages in young, healthy adults who habitually consume caffeine. Further, serum caffeine concentration was not different between sublingual mouth spray and the ingestion of caffeinated beverages throughout the 90 min following consumption. This absence of a difference in serum caffeine concentration between the caffeine types assessed was associated with no difference in the improvements to cognitive performance or increase of blood pressure.

The caffeine mouth spray was tested presuming caffeine would be absorbed in the buccal cavity and thereby blood caffeine would be increased sooner compared to absorption via digestion. The similar serum caffeine concentration by time profile and peak serum caffeine concentration of caffeine mouth spray compared to caffeinated beverages suggests that the mechanisms of caffeine absorption were also similar between the administration methods. The caffeine mouth-spray liquid was held sublingually for ~ 2 min, which may have been insufficient to elicit meaningful oral absorption. More caffeine was absorbed into circulation from caffeine chewing gum when chewed for 10 vs. 5 vs. 2 min (Syed et al. 2005), though it is unclear if this effect was related to a longer buccal exposure per se or also involved greater release of caffeine from the gum due to more mechanical release from chewing. Future work could test a caffeine mouth-spray delivery system with longer oral exposure times and/or application to the buccal mucosa rather than sublingual.

While it was observed that serum caffeine concentration did not increase faster after caffeinated mouth spray compared to beverages, this may not be the same for caffeine capsules. A study examined oral absorption of caffeine into circulation using chewing gum and reported a faster time-to-peak concentration compared to ingestion of capsules (Kamimori et al. 2002), but this difference was not observed when compared to a caffeinated beverage (Sadek et al. 2017). This may indicate that there are differences between caffeine absorption between capsules and beverages. In support, we observed a serum caffeine concentration of ~ 1 mg/L 30 min after ingesting ~ 60 mg of caffeine, while Kamimori et al. (2002) reported a similar blood caffeine 30 min after ingesting a capsule containing ~ 3.3-fold more caffeine (200 mg) than what was administered herein. A potentially faster caffeine absorption following caffeinated beverages than capsules may suggest some buccal absorption of caffeine occurs in the process of ingesting beverages. Though it must be directly tested, caffeinated mouth spray could increase blood caffeine faster than caffeine capsules. Understanding the time-course blood caffeine response to caffeine mouth sprays and capsules may be desirable by users wanting a light, portable, and easy to administer caffeine product.

The observation that the type of caffeine administered did not influence any cognitive or hemodynamic variables measured aligned with the blood caffeine data. Cognitive function was assessed 30 min after caffeine use in an attempt to assess functional consequences of caffeine at the expected peak blood concentration in the mouth-spray condition and minimally increased caffeine in the caffeinated beverage conditions. However, as discussed above, this separation of blood caffeine concentration at ~ 30-min post-caffeine use between conditions did not occur. The improvement to cognitive function after caffeine use compared to baseline were seemingly small as the magnitude of such approached day-to-day variability of the tests. While previous work has shown that caffeine can improve cognitive function (McLellan et al. 2016), it must be noted that the study design did not permit isolation of a direct effect of caffeine. As Tallis et al. (2022) noted previously, more research is required to understand dose–response and time-based effects of caffeine on cognition and hemodynamics.

A limitation of this study was that it was designed to primarily probe whether caffeine administration method altered the expected effects of caffeine, and therefore it was not possible to parse out the relative influences of caffeine, placebo, and time of day on any temporal changes in cognitive and hemodynamic variables. Second, while the study design considered mechanisms of caffeine absorption from caffeine gum, this intervention was not assessed. A direct comparison between caffeinated gums and mouth sprays for equivalence or non-inferiority would be worthwhile after optimal administration instructions for the mouth spray (e.g., time in mouth, dose–response) are uncovered. Third, the current findings may not generalize to all mouth sprays, as formulations can vary across different products, or larger doses of caffeine. Finally, certain cognitive responses to caffeine may differ in habitual and non-habitual caffeine users, therefore the cognitive effects herein may depend on habitual caffeine use (Haskell et al. 2005). Though, from an applied perspective, the effects of caffeine on endurance performance do not seem to depend on habitual caffeine use (Antonio et al. 2024, Clark and Richardson 2021).

In conclusion, sublingual administration of caffeine via mouth spray did not result in faster appearance of caffeine into the bloodstream compared to caffeinated beverages. Blood caffeine concentration increased after using the caffeine mouth spray similar to ingestion of caffeinated beverages, which could indicate that the majority of caffeine is absorbed in the intestines after swallowing the liquid rather than through sublingual absorption. This work suggests that sublingual administration of caffeine via novel mouth spray may not provide a benefit over more traditional caffeinated beverages in terms of caffeine bioavailability or cognitive function. However, this caffeine mouth-spray product seems to be a viable option for individuals seeking to increase blood caffeine levels, and may be more practical than beverages in certain situations where ingesting lager volumes of liquid is not practical or desired, e.g., long-duration and/or weight sensitive activities. Future work could test the efficacy of this caffeine administration method as an ergogenic aid to determine whether it is a viable option for athletes and compare its efficacy and pharmacokinetics to caffeinated gum.

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Author contributions D.G.M., P.J.M., and J.F.B. contributed to study conception and experimental design; D.G.M., R.K.S., S.A., and S.T. conducted experiments; R.H. analyzed blood samples; D.G.M., R.K.S., and R.H. analyzed data; D.G.M. drafted the manuscript; all authors contributed to manuscript editing and approved the manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

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