**Supplementary Materials**

**2. Methods**

**2.1 Subjects**

Exclusion criteria were the following: evidence of a preexisting condition that may alter the absorption, distribution, metabolism or excretion of alcohol or EDs, psychiatric disorders, alcoholism, abuse of prescription drugs or illegal substances or regular consumption of psychoactive drugs, smokers of >5 cigarettes/day, consumption of >40 g/day of alcohol and daily consumption of more than 5 methylxanthine-containing products. Prior to their inclusion, participants were submitted to a general medical examination, including blood laboratory tests (serology for hepatitis B, C and human immunodeficiency viruses included), a urinalysis and an electrocardiogram. To discard recent consumption of drugs and alcohol, alcohol in exhaled air was measured and drug urine tests were performed (amphetamines, benzodiazepines, cocaine, morphine and tetrahydrocannabinol) at screening and baseline in each experimental session. Alcohol Use Disorders Identification Test was used as a screener and if ≥13 points were obtained a detailed psychiatric interview was performed to exclude participants with alcohol use disorders. All tests were performed to assure that volunteers included do not have any medical condition that could interfere with alcohol or EDs pharmacokinetics or that represents a higher risk for their participation.

**2.4 Driving related skills**

The SRT task measures the simple reaction time with a delivery of a known stimulus (white square) in a known location of the screen to provoke a known answer (pushing a button). Participants should response to each stimulus as quickly as possible. A total of 60 stimuli are shown each time the test is administered. Outcome measures cover latency (response speed), latency standard deviation (SD), correct responses and errors of commission and omission. Test duration is 6 minutes. The task used is included in Cambridge Neuropsychological Test Automated Battery (Simple Reaction Time).

The NB task (Gevins and Cutillo, 1993) allows studying the visual-motor answers in the context of processes related with the working memory. The task requires an update and manipulation of

the remembered information. It consists in remembering a previous visual stimulus in function of the n charge. In other words, in a 0-back task, subjects have to remember the stimulus that has just appeared, in the 1-back task they have to remember the penultimate stimulus and successively. The participant must push one of the mouse buttons related of the n charge. Our stimuli were numbers from 1 to 4 and included two 0-back and two 2-back modules along 155 seconds (56 total hits: 30 hits of 0-back and 26 hits of 2-back mode). Reaction time, hits, missings and errors were registered.

The MET measures the capacity of the subject to estimate the speed of an object in movement or the estimation of the time that takes an object in movement to arrive to a location. It's an interactive task where a vehicle, which circulates in a constant velocity during a fix period of time, enters in a tunnel where it can't be seen or arrives to a fixed point on the screen. The subject must estimate the time when the vehicle arrives to the marked point on the street or when it arrives to the end of the tunnel pushing a button. It registers the absolute error time, which is the mean of the absolute difference between the estimated time and the real time that it takes the vehicle to surpass the tunnel. Also, it measures the error time taking into account anticipations (negative values) and delays (positive values). The test is administered in 380 seconds. It also measures missing values. This task was chosen because it is very similar to the Anticipation of Speed Test used in Spain to obtain the driving license (Gombao et al., 2006).

### 2.8 Analytical Assays

**Analytical procedure for taurine and caffeine analysis in plasma**

In order to precipitate proteins, a 100 µl aliquot of plasma with 150 µl of cold acetonitrile was transferred into an Eppendorf® LoBind microcentrifuge tube and was mixed by pulse-vortexing for some seconds. After centrifugation (10.000rpm for 10 min at 4ºC), the organic phase was transferred into a new glass tube. Aliquots were spiked with 10 µL of IS mix solution (containing 10 µg/mL of d3-Caffeine and 100 µg/mL of d4-Taurine).

A derivatization step with 200 µl FMOC-CL 3mM (9-fluoroenilmethyl chloroformiate) and 200 µl Potassium Borate buffer at pH 8.5 (Brückner et al., 2012; Sancho et al., 1994) was needed to increase the detection of taurine compound. After evaporate the organic portion to dryness

under a nitrogen stream at 29ºC >15 psi, samples were reconstituted with 2 mL of MilliQ water previous a clean-up process with a solid phase extraction.  Aliquots were passed through an Oasis® HLB 3 cc Vac Cartridge, 60 mg, 30 µm particle size. Columns were rinsed with 2 mL of MilliQ water and eluted with 2mL of acetonitrile. The eluted samples were evaporated under nitrogen stream at 29ºC <15psi. Extracts were reconstituted with 500µl 90:10 (H2O HCOOH 0.1%: ACN HCOOH 0.1%).

Identification and quantification analyses were performed with an Agilent 1200 series HPLC system (Agilent Technologies, Wilmington, DE) coupled to a triple quadrupole (6410 Triple Quad LC/MS; Agilent) mass spectrometer with an electrospray interface. The liquid chromatographic separation was performed using an ACQUITY UPLC HSS T3 Column (100 mm×2.1 mm i.d., 1.8µm particle size) from Waters Corporation (Milford, MA, USA) maintained at 40ºC with a column oven. The composition of the mobile phase A was 0.01% (v/v) formic acid in water, and mobile phase B was 0.01% (v/v) formic acid in acetonitrile.

Initial conditions of the mobile phase were 10% of B. After that, it was linearly increased to 100% of B over 1 min and it was maintained for 3min. Gradient was return to initial conditions within 0.1min and then it was hold with 10% of B during 6 minutes. The total run time was 10 min at a flow rate of 0.225 mL/min. The injection volume was 1µL. The ion source was operated in negative ionization mode for taurine and in positive for caffeine segment.

Precursor ions and product ions for both compounds and its internal standards were selected. Precursor ions used to quantify were 346 m/z and 350 m/z for taurine and d4-Taurine and 195 m/z and 198 m/z for caffeine and d3-caffeine. Product ions selected were 167.9 m/z and 124 m/z for taurine and 172 m/z and 128 m/z for d4-Taurine. On caffeine condition, product ions were 138 m/z and 110 m/z, and 140 m/z and 112 m/z for its internal standard.

Calibration standards of taurine and caffeine were prepared for each analytical batch which consisted of two replicates at 6 different concentrations (2.5, 5, 10, 25 and 50 µg/mL for taurine, and 0.25, 0.5, 1, 2.5 and 5µg/ml for caffeine).

Quality control (QC) samples were prepared fortifying blank plasma at four concentrations (2.5, 9, 28 and 47µg/mL) for taurine and (0.25, 0.9, 3 and 4.6µg/mL) for caffeine in plasma. QCs were kept at -20 °C until analyses.

Recovery and matrix effect were evaluated from six different sources in triplicate at two different concentrations (low and high concentrations). Quantitative extraction recoveries (77% and 102%) and matrix effects (-49% and -29%) for taurine and caffeine respectively, were found for both compounds. The limits of detection (LOD) and quantification (LOQ) for taurine were 1.1µg/mL and 3.3 µg/mL, respectively. For caffeine, the LOD and LOQ were 0.1µg/mL and 0.2µg/mL.

Other methods are available elsewhere to detect concentrations of methylxanthines in dietary supplements (Marchei et al., 2005).

**Analytical procedure for caffeine and metabolites analysis in urine**

Caffeine, paraxanthine, theobromine, theophylline and 1,3,7-trimethyluric acid were analyzed in urine as follows by GC/MS. Briefly, 0.5ml of urine was submitted to a liquid-liquid extraction by addition of 250 µl of potassium carbonate 5% and 6 mL of tert-butylmethylether. The organic layer was evaporated after centrifugation and samples were derivatized with 50 µL of MSTFA-NH4I-mercaptoethanol (1000:2:6, v/w/v) by heating at 60 °C for 30 minutes, and transferred to the injection vial. GC–MS analyses were carried out with an Agilent 6890 Series gas chromatograph equipped with an Agilent 7683 autosampler and coupled to a 5973N mass selective detector (Agilent Technologies, Palo Alto, CA, USA). Separation was carried out with a cross-linked 5% phenylmethylsiloxane capillary column (ZB-5MS, Zebron Capillary GC Column, Phenomenex; California, USA). Helium was used as carrier gas at an initial flow rate of 1.2 mL/min under a constant pressure of 12 psi. Calibration standards of caffeine and its metabolites were prepared for each analytical batch which consisted of two replicates at 5 different concentrations (0.06, 0.1, 1, 6 and 10 µg/ml. Caffeine-d3 was used as internal standard. Limits of detection were between 11.5and 19.8 ng/mL and of quantification between 34.8 and 59.9 ng/mL for the compounds analyzed.

**2.10 Statistical Analysis**

**Sample size calculation**

Sample size was calculated following the methodology of the bioequivalence studies, taking an alpha risk of 0.05, a power of 80%, a variability of 20% and a difference in the time outside the road (TimeOut) of at least 20%, 16 subjects would be needed.

Brückner H, Flassig S, Kirschbaum J (2012) Determination of biogenic amines in infusions of tea (Camellia sinensis) by HPLC after derivatization with 9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl). Amino Acids 42:877-85.

Gevins AS, Cutillo BC (1993) Neuroelectric evidence for distributed processing in human working memory. Electroencephalogr Clin Neurophysiol 87:128-143.

Gombao JC, Muñoz A, Monterde H (2006) El Reconocimiento Psicológico Oficial para la Licencia de Armas y Carnet de Conducir con el Equipo LND. LNDeter SA, Madrid, Spain.

Marchei E, Pellegrini M, Pacifici R, Palmi I, Pichini S (2005) Development and validation of a high performance liquid chromatography-mass spectometry assay for methylxanthines and taurine in dietary supplements. J Pharm Biomed Anal 37:499-507

Sancho JV, López FJ, Hernández F, Hogendoorn EA, van Zoonen P (1994) Rapid determination of glufosinate in environmental water samples using 9-fluorenylmethoxycarbonyl precolumn derivatization, large-volume injection and coupled-column liquid chromatography. Journal of Chromatography A. 678:59-67.

**Supplementary figures**

Figure S1. Flow chart of participants.

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┌─────────────────┐
│    Contacted    │
│      n=63       │
└────────┬────────┘
         │              ┌──────────────────────────────────┐
         ├─────────────>│ Did not meet protocol criteria n=23 or │
         │              │   unwilling to participate n=24   │
         ▼              └──────────────────────────────────┘
┌─────────────────┐
│    Screened     │
│      n=16       │
└────────┬────────┘
         │              ┌──────────────────────────────────┐
         ├─────────────>│ Did not meet protocol criteria or │
         │              │   unwilling to participate n=0    │
         ▼              └──────────────────────────────────┘
┌─────────────────┐
│ Randomly assigned │
│      n=16       │
└────────┬────────┘
         │              ┌──────────────────────────────────┐
         ├─────────────>│ Discontinued due to an adverse    │
         │              │          event n=0                │
         ▼              └──────────────────────────────────┘
┌─────────────────┐
│ Completed the study │
│      n=16       │
└─────────────────┘
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