SUPPLEMENTARY MATERIAL

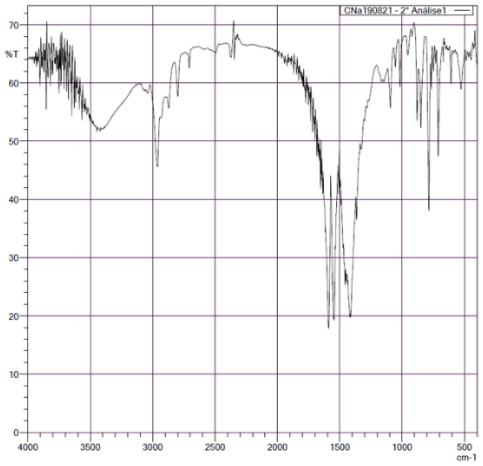
Table S1. Purity by Gas Chromatography (GC, %) and retention time (RT, min) of the commercial compounds tested and of their other constituents.

Compound	Content by GC (%) and RT (min, between parentheses)			
	Certified by supplier	Determined	Main minor constituents	RT of other minor constituents
p-Cymene	99.4	99.6 (4.63)	0.4 (4.10)	-
Cuminaldehyde	99.3	97.8 (7.88)	2.0 (12.51)	(7.63)
Cuminol	96.9	97.6 (9.42)	1.6 (7.86)	(9.23), (9.33)
Cuminic acid	98.9	97.2 (12.52)	2.5 (13.96)	(5.74)

Fourier-transform infrared spectrometry (FTIR) of the sodium cuminate

The characteristic FTIR frequency bands of an unsaturated organic acid salt [1] were observed in the synthetized sodium cuminate (Figure S1a): stretching (ν) C-H (ν_{C-H}) in 2800-3000 cm^{-1}, ν_{C-C} at 1589 cm^{-1} relative to axial deformation of the aromatic ring, asymmetric and symmetric axial deformation of carboxylate anion at 1545-1555 cm^{-1} and 1410-1450 cm^{-1}, respectively, and at 1095 cm^{-1} relative to ν_{C-O}. It is notable that the asymmetrical C=O band in 1685 cm^{-1} of cuminic acid (Figure S1b), characteristic of carboxylic carbonyl group in conjugation with unsaturation, was not observed in the salt chemical entity given way to the typical strong asymmetrical stretching band of the carboxylate ion (1589 cm^{-1}, Figure S1a), as would be expected.

(a)



(b)

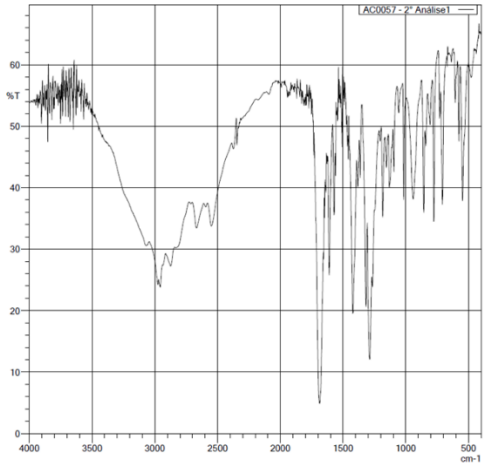


Figure S1. FTIR spectra of sodium cuminate (a) and cuminic acid (b).

Thermogravimetric analysis (TGA) of the sodium cuminate

By analyzing the profile of the TGA curves of the cuminic acid and sodium cuminate (Figure S2), the salt at 92.33°C lost 3.2% of moisture, then remaining constant until 350°C, and thus, demonstrating the absence of cuminic acid residue which has a melting point between 117 - 118°C (PubChem, pubchem.ncbi.nlm.nih.gov).

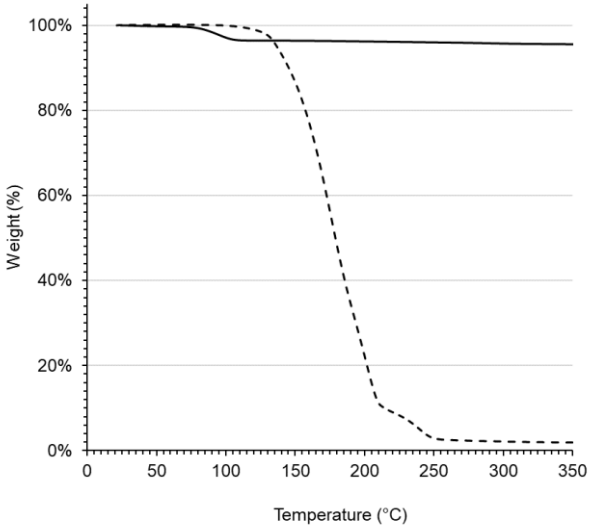


Figure S2. TGA thermograms of sodium cuminate (solid line) and cuminic acid (dashed line).

ADMET

The physicochemical and drug-likeness properties obtained from the SwissADME and ADMETlab servers are shown in Table S2. The molecular descriptors were checked in accordance with the theoretical values: molecular formula, molecular weight (MW), hydrogen-bond donors (HBD), hydrogen-bond acceptors (HBA), and the quantity of rotatable bonds (nRotB) (both servers), atoms (nAtom), carbon atoms (nCarbon) (SwissADME), heteroatoms (nHet), and rings (nRing) (ADMETlab). This verification validates the drug-likeness requirement rules (Table S2): Lipinski, MW ≤ 500, HBD ≤ 5, HBA ≤ 10, Log P ≤ 5 or MLog P ≤ 4.15; Ghose, 160 ≤ MW ≤ 480, − 0.4 ≤ WLog P ≤ 5.6, 40 ≤ MR ≤ 130, 20 ≤ nAtom ≤ 70; Veber, nRotB ≤ 10, TPSA ≤ 140 $Å^2$; Egan, WLog P ≤ 5.88, TPSA ≤ 131.6 $Å^2$; Muegge, 200 ≤ MW ≤ 600, HBD ≤ 5, HBA ≤ 10, −2 ≤ XLog P ≤ 5, TPSA ≤ 150 $Å^2$, nAtom ≤ 7, nCarbon > 4, nHet > 1, nRotB ≤ 15; Pfizer, Log P > 3, TPSA < 75 $Å^2$; GSK, MW ≤ 400, Log P ≤ 4; and Golden Triangle, 50 ≤ MW ≤ 200, -2 ≤ Log D7.4 ≤ 5.

Table S2. Prediction of physicochemical properties and drug-likeness parameters from the SwissADME and ADMETlab servers

Descriptors	*p*-Cymene	Cuminaldehyde	Cuminic acid	Cuminol	Sodium cuminate
Log P [1,2]	2.51	2.03	1.85	2.33	-10.38
Log P [3]	3.99	2.89	3.28	2.41	1.12
WLog P [2]	3.12	3.62	2.51	2.15	1.17
XLog P [2]	4.10	2.37	3.40	2.34	3.40
MLog P [2]	4.47	2.40	2.55	2.49	2.55
Log D7.4 [3]	2.80	3.78	2.36	2.45	0.48
MR [2]	46.0	46.4	48.0	47.1	46.0
TPSA	0	17.1	37.3	20.2	40.1
Lipinski, Veber [2], Egan [2], and GSK [3]	Yes	Yes	Yes	Yes	Yes
Pfizer [3]	No	Yes	No	Yes	Yes
Ghose [2]	No	No	Yes	No	Yes
Muegge [2] and Golden Triangle [3]	No	No	No	No	No

[1]Lipophylicity predicted through the logarithm of the partition/distribution coefficients between *n*-octanol and water (Log P), using atomistic method based on the fragmental system (WLog P) and knowledge-based method calculated by XLOG P Program (XLog P); using the Moriguchi (MLog P) method through neural networks; or of *n*-octanol/buffer solution at pH 7.4 (Log D7.4). MR: molecular refractivity. TPSA: topological polar surface area. Determined only from [2]SwissADME or [3]ADMETlab.

Table S3. Prediction of human pharmacological properties of absorption and distribution from SwissADME and ADMETlab servers

Parameters[1]	*p*-Cymene	Cuminaldehyde	Cuminic acid	Cuminol	Sodium cuminate
HIA[2]	Low/Excellent[3]	High/Excellent	High/Excellent	High/Excellent	High/Excellent
BBB Permeability (log BBB, cm/s)[2]	Yes/4 [3]	Yes/5	Yes/1	Yes/5	Yes/1
Skin Permeability (log Kp, cm/s)[2,4]	-4.21	-5.52	-4.89	-5.55	-5.02
Caco-2 permeability (log cm/s)[5]	-4.30	-4.36	-4.59	-4.13	-4.37
MDCK permeability (10^{-5} log cm/s)[5]	2.0	2.5	2.2	1.9	3.7
Pgp inhibitor[5]	No/0	No/0	No/0	No/0	No/0
Pgp substrate	No/0	No/0	No/0	No/0	Yes/0
VDss (L/Kg)[5]	2.14	1.18	0.22	2.35	0.35
Binding to plasma proteins (%)[5]	94.4	88.6	88.2	82.0	89.2
Fraction unbound in plasma (%)[5]	6.1	10.9	12.4	19.9	10.9

[1]HIA, Human (gastro)intestinal absorption; BBB, blood-brain barrier (BBB); MDCK, Madin−Darby Canine Kidney cells; Pgp, P-glycoprotein; and VDss, volume distribution at steady state. [2]Determined from SwissADME through the the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg). [3]Probability separated by slash: SwissADME/ADMETlab. SwissADME: No or Yes; ADMETlab: - (not indicated), 0 (0-10%), 1 (10-30%), 2 (30-50%), 3 (50-70%), 4 (70-90%), or 5 (90-100%). Determined only from [4]SwissADME or [5]ADMETlab.

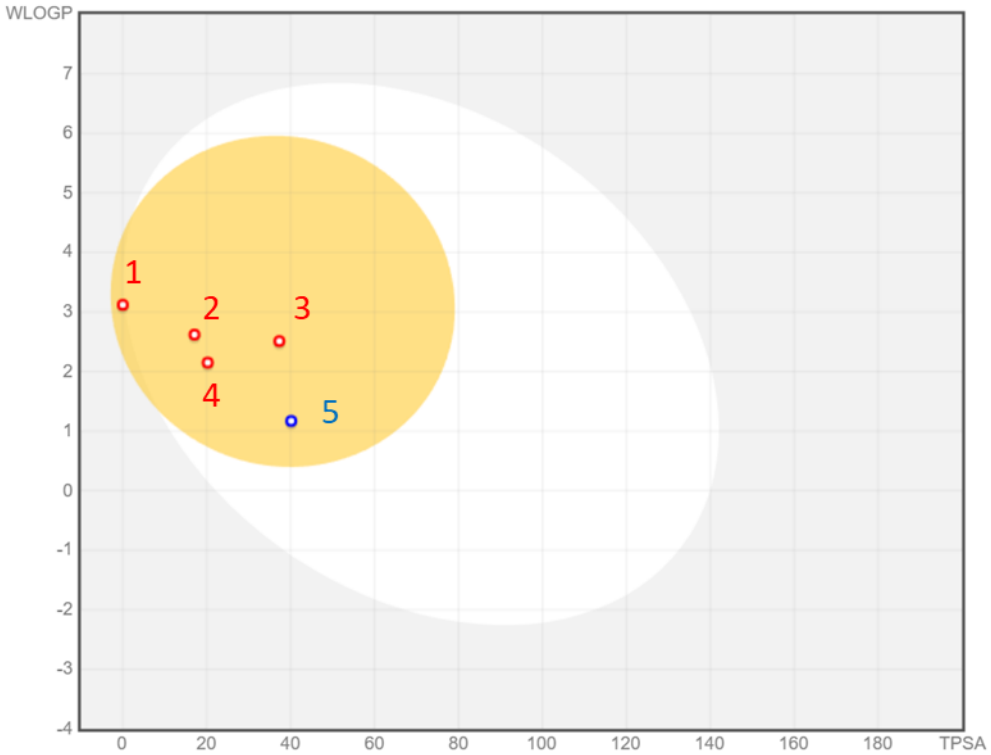


Figure S3. Diagram of Brain Or IntestinaL EstimateD (BOILED-Egg) permeation by the SwissADME server for the compounds in study. 1, *p*-Cymene; 2, cuminaldehyde; 3, cuminic acid; 4, cuminol; and 5, sodium cuminate. The yellow area of the egg yolk represents the limit of the properties relative to BBB passage, while the white region of the egg yolk defines the properties with a high probability of passive human intestinal absorption (HIA). Compounds predicted being non-substrates of Pgp (PGP-) are represented by red dots, while the one predicted being effluxed actively from the central nervous system (CNS) by Pgp (PGP+) is represented by a blue dot (swissadme.ch/index.php).

Table S4. Induction and inhibition of human cytochromes P450 (CYP) enzymes

Descriptors	*p*-Cymene	Cuminaldehyde	Cuminic acid	Cuminol	Sodium cuminate
Inhibitor					
CYP1A2	No/5/1 [1]	Yes/5/-	No/1/-	Yes/4/-	No/0/-
CYP2C19	No/4/2	No/3/1	No/0/1	No/3/2	No/0/-
CYP2C9	No/3/1	No/1/-	No/1/2	No/1/1	No/1/-
CYP2D6	Yes/4/1	No/0/-	No/0/-	No/4/1	No/0/-
CYP3A4	No/0/1	No/0/-	No/0/-	No/0/1	No/0/-
CYP26A1 [2]	0	-	0	0	-
CYP26B1 [2]	1	0	1	1	-
CYP2A13 [2]	4	2	3	3	-
CYP2A6 [2]	0	0	-	-	-
CYP2B6 [2]	1	1	1	1	-
CYP2J2 [2]	1	-	1	1	-
CYP3A7 [2]	2	-	1	1	-
CYP4Z1 [2]	0	0	0	0	-
Substrate					
CYP1A2 [3]	5	3	2	5	1
CYP2C19 [3]	4	3	0	3	2
CYP2C9 [3]	3	3	1	1	2
CYP2D6 [3]	4	2	0	3	0
CYP3A4 [3]	3	2	1	3	1
CYP2B6 [2]	1	-	1	-	-

[1]Probability separated by slash: SwissADME/ADMETlab/CLC-Pred. SwissADME: No or Yes; ADMETlab and CLC-Pred: - (not indicated), 0 (0-10%), 1 (10-30%), 2 (30-50%), 3 (50-70%), 4 (70-90%), or 5 (90-100%). Determined only by [2]CLC-Pred or also [3]ADMETlab.

Toxicity

The toxicological parameters were negatives by all compounds through the computational prediction for major of toxicity assays, endpoints, adverse outcomes pathways (Tox21 datasets, toxicology in the 21st Century), and toxicity targets. Table S5 shows only the risks of toxicity with probability ≥ 50%.

Table S5. Positive toxicological risks predicted through ADMETlab and Protox-II servers (probability ≥ 50%).

Compound	ADMETlab	Protox-II
p-Cymene	No	Carcinogenic / class I
Cuminaldehyde	No	No / class IV
Cuminic acid	DILI [1]	DILI / class IV
Cuminol	No	No / class IV
Sodium cuminate	DILI / H-TH [2]	class IV

[1]DILI, Drug Induced Liver Injury. [2]Human hepatotoxicity.

References

1. Silverstein RM, Bassler C G, Morrill, Terence C (1981). Spectrometric identification of organic compounds. 4th ed. Singapore: John Wiley & Sons, cap. 3.