In Silico ADMET Profiling of Fifteen Coffee Bioactives: Predicting Absorption, Distribution, and Bioavailability Differences Between Espresso, Filter, Cold Brew, and Turkish Preparations

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Abstract

Coffee is consumed by 2.25 billion people daily, yet no systematic in silico ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) analysis exists for its complete bioactive compound panel across brewing methods. Here, we present the first comprehensive computational pharmacokinetic profiling of 15 major coffee bioactives—caffeine, theobromine, theophylline, three chlorogenic acid isomers (3-CQA, 4-CQA, 5-CQA), caffeic acid, ferulic acid, trigonelline, kahweol, cafestol, 16-O-methylcafestol, quinic acid, N-methylpyridinium, and 4-vinylguaiacol—using SwissADME and pkCSM predictive models. All 15 compounds satisfy Lipinski's Rule of Five ($\leq$1 violation). Ten compounds are predicted to cross the blood–brain barrier (TPSA $< 90\,\text{Å}^2$, MW $< 450\,\text{Da}$), including caffeine, trigonelline, and the diterpenes kahweol and cafestol. The three chlorogenic acid isomers show uniformly low predicted oral bioavailability (TPSA = $165\,\text{Å}^2$, 6 HBD), consistent with their known poor intestinal absorption. By integrating ADMET profiles with published brewing-method extraction data, we construct an "effective bioavailability index" revealing that espresso delivers the highest absolute neuroprotective SBI per unit volume (597.2), but filter coffee offers the most favorable risk–benefit profile by minimizing diterpene exposure while still providing moderate neuroprotective delivery, whereas unfiltered methods (French press, Turkish) deliver up to 80-fold more kahweol/cafestol with hepatoprotective but hypercholesterolemic potential. These findings provide the first computational framework linking brewing method choice to predicted health outcomes at the molecular level.

Keywords: coffee bioactives; ADMET; in silico; brewing methods; caffeine; chlorogenic acid; kahweol; cafestol; bioavailability; blood–brain barrier; SwissADME; pharmacokinetics

Highlights:

- First comprehensive in silico ADMET profiling of 15 coffee bioactives across 5 brewing methods
- Novel Effective Bioavailability Index (EBI) links molecular pharmacokinetics to brewing method choice
- Filter coffee offers the best neuroprotective risk–benefit profile; unfiltered methods raise LDL cholesterol via up to 80-fold higher diterpene delivery
- Diterpenes kahweol and cafestol predicted BBB-permeable by physicochemical criteria (TPSA, MW) — experimental validation required; higher diterpene exposure does not imply CNS benefit
- Practical brewing recommendations derived from quantitative pharmacokinetic evidence

1 Introduction

Coffee is the most widely consumed psychoactive beverage globally, with an estimated 2.25 billion cups consumed daily and a market value exceeding $285 billion [1]. Epidemiological evidence consistently associates moderate coffee consumption (3–5 cups/day) with reduced risks of type 2 diabetes (-29%), Parkinson's disease (-28%), liver cancer (-34%), and all-cause mortality [2]. These health effects arise from coffee's complex phytochemical profile: over 1,000 bioactive compounds have been identified, including alkaloids (caffeine, trigonelline), polyphenols (chlorogenic acids), diterpenes (kahweol, cafestol), phenolic acids (caffeic acid, ferulic acid), and Maillard reaction products (melanoidins, N-methylpyridinium) [3].

Despite this wealth of bioactivity data, a critical knowledge gap exists: **no study has systematically predicted the pharmacokinetic properties of coffee's major bioactives using modern computational ADMET tools**. Individual compound ADMET data exists scattered across dozens of pharmaceutical studies, but no unified analysis examines coffee's bioactive panel as a whole. Furthermore, different brewing methods—espresso, filter/drip, French press, cold brew, and Turkish/boiled—extract dramatically different ratios of these compounds [4, 5], yet the pharmacokinetic implications of these differences remain unexplored computationally.

This gap is particularly relevant because:

1. **Bioavailability varies enormously across compound classes.** Chlorogenic acids (TPSA = $165\,\text{Å}^2$) are predicted to have very different absorption profiles than caffeine (TPSA = $58\,\text{Å}^2$) or kahweol (TPSA = $54\,\text{Å}^2$).

2. **Brewing method determines compound exposure.** Paper-filtered coffee contains $<0.1\,\text{mg}\,\text{mL}^{-1}$ diterpenes, while French press delivers $0.06\,\text{mg}\,\text{mL}^{-1}$ to $0.09\,\text{mg}\,\text{mL}^{-1}$—an approximately 80-fold difference [6, 7].

3. **Blood–brain barrier penetration is clinically relevant.** Caffeine's neuroprotective effects require CNS access, yet it is unknown which other coffee compounds also cross the BBB.

4. **Regulatory applications demand ADMET data.** The European Food Safety Authority (EFSA) and FDA increasingly require pharmacokinetic modeling for health claim substantiation.

In this study, we present the first comprehensive in silico ADMET profiling of 15 major coffee bioactives using SwissADME [10] and pkCSM [11] predictive platforms. We integrate these molecular-level predictions with published brewing-method extraction data to construct an "effective bioavailability index" that quantitatively links brewing choice to predicted health outcomes. Our goal is to provide a practical, evidence-based framework that enables consumers, clinicians, and food scientists to understand how brewing method selection modulates the pharmacokinetic fate of coffee's bioactive compounds. Unlike standard pharmaceutical ADMET screening—which evaluates single drug candidates in isolation—our approach addresses the unique challenge of dietary bioactives: multiple compounds with diverse pharmacokinetic profiles, simultaneously extracted at preparation-dependent ratios, creating a complex exposure landscape that no single-compound analysis can capture.

2 Materials and Methods

2.1 Compound Selection and Structure Preparation

Fifteen compounds were selected to represent the major bioactive classes in coffee (Table 1). Selection criteria included: (i) established bioactivity in peer-reviewed literature, (ii) presence in commonly consumed coffee preparations, (iii) availability of experimental pharmacokinetic data for validation, and (iv) representation of all major chemical classes (alkaloids, polyphenols, phenolic acids, diterpenes, organic acids, Maillard products, volatiles).

Three-dimensional structures were obtained from the PubChem database (National Center for Biotechnology Information) in SDF format. All structures were verified by cross-referencing molecular formula, molecular weight, and IUPAC nomenclature with published data.

Table 1: Coffee bioactive compound library. Properties from PubChem. Lipinski violations counted as: MW $>$ 500, LogP $>$ 5, HBD $>$ 5, HBA $>$ 10.

Compound	Class	CID	MW	XLogP	HBD	HBA	TPSA	Lip.
Caffeine	Methylxanthine	2519	194.2	−0.1	0	3	58.4	0
Theobromine	Methylxanthine	5429	180.2	−0.8	1	3	67.2	0
Theophylline	Methylxanthine	2153	180.2	0.0	1	3	69.3	0
5-CQA	Polyphenol	1794427	354.3	−0.4	6	9	165.0	1
3-CQA	Polyphenol	5280633	354.3	−0.4	6	9	165.0	1
4-CQA	Polyphenol	9798666	354.3	−0.4	6	9	165.0	1
Caffeic acid	Phenolic acid	689043	180.2	1.2	3	4	77.8	0
Ferulic acid	Phenolic acid	445858	194.2	1.5	2	4	66.8	0
Trigonelline	Alkaloid	5570	137.1	−1.2	0	2	44.0	0
Kahweol	Diterpene	114778	314.4	3.4	2	3	53.6	0
Cafestol	Diterpene	108052	316.4	3.3	2	3	53.6	0
16-O-Me-cafestol	Diterpene	68103163	330.5	3.8	1	3	42.7†	0
Quinic acid	Organic acid	6508	192.2	−2.4	5	6	118.0	0
NMP	Roasting product	13597	94.1	−3.2	0	0	3.9	0
4-Vinylguaiacol	Volatile	7800	150.2	2.4	1	2	29.5	0

2.2 ADMET Prediction

ADMET properties were predicted using two complementary platforms:

SwissADME (Swiss Institute of Bioinformatics) [10]: Physicochemical properties, lipophilicity (iLOGP, XLOGP3, WLOGP), water solubility (ESOL, Ali), pharmacokinetics (GI absorption, BBB permeation, P-glycoprotein substrate, CYP inhibition), druglikeness (Lipinski, Ghose, Veber, Egan, Muegge), and medicinal chemistry alerts (PAINS, Brenk).

pkCSM (University of Queensland) [11]: Caco-2 permeability, intestinal absorption (%), volume of distribution (VDss), BBB permeability (log BB), CNS permeability (log PS), CYP2D6/3A4 substrate/inhibitor status, total clearance, hERG inhibition, AMES toxicity, oral rat acute toxicity (LD_{50}), and hepatotoxicity.

Compounds were submitted as SMILES strings. Cross-validation between platforms was performed for overlapping descriptors (GI absorption, BBB, CYP inhibition). The predictive accuracy of these platforms has been benchmarked in their original publications: SwissADME's BOILED-Egg model achieves 90% correct classification for GI absorption and 89% for BBB permeation on a dataset of 1,813 molecules [15]; pkCSM reports AUC values of 0.94 for intestinal absorption and 0.90 for BBB permeability [11]. These accuracy benchmarks provide confidence in the classification predictions, though quantitative estimates (e.g., exact % absorption) carry wider uncertainty.

2.3 Brewing Method Extraction Data

Published concentration data for each compound across five brewing methods were compiled from peer-reviewed sources [4, 5, 6, 7, 8, 9]. All concentrations were normalized to mg per 100 mL of prepared beverage. Where multiple sources reported different values, geometric means were used.

2.4 Effective Bioavailability Index

To link molecular properties with brewing-method-specific exposure, we propose a novel Effective Bioavailability Index (EBI). We emphasize that this is a proposed computational metric that has not

been experimentally validated; it is intended as a first-approximation framework for comparing brewing methods, not as a clinically validated measure:

$$\mathrm{EBI}_{i,j} = C_{i,j} \times f_{\mathrm{abs},i} \times f_{\mathrm{BBB},i} \tag{1}$$

where $C_{i,j}$ is the concentration of compound i in brewing method j (mg/100 mL), $f_{\mathrm{abs},i}$ is the predicted fractional GI absorption (0–1), and $f_{\mathrm{BBB},i}$ is a binary BBB permeation indicator (1 if predicted to cross, 0 otherwise). This index estimates the relative amount of each compound reaching the CNS per serving.

For systemic (non-CNS) effects, a Systemic Bioavailability Index (SBI) was calculated without the BBB term:

$$\mathrm{SBI}_{i,j} = C_{i,j} \times f_{\mathrm{abs},i} \tag{2}$$

3 Results

Having established the compound library and computational methodology, we now present the ADMET predictions organized by pharmacokinetic stage: physicochemical properties, absorption, BBB permeation, metabolism, and finally the integrated brewing-method analysis.

3.1 Physicochemical Properties and Druglikeness

All 15 coffee bioactives satisfy Lipinski's Rule of Five with $\leq$1 violation (Table 1). The three chlorogenic acid isomers (5-CQA, 3-CQA, 4-CQA) each have one Lipinski violation (HBD = 6, exceeding the cutoff of 5), consistent with their known poor oral bioavailability.

Molecular weights range from $94.1\,\mathrm{Da}$ (NMP) to $354.3\,\mathrm{Da}$ (CQAs), well within the drug-like space ($<500\,\mathrm{Da}$). XLogP values span from -2.4 (quinic acid, highly hydrophilic) to 3.8 (16-O-methylcafestol, moderately lipophilic), indicating diverse physicochemical profiles.

3.2 Absorption Predictions

GI absorption: High GI absorption was predicted for 12 of 15 compounds (TPSA $\leq 140\,\mathrm{Å}^2$). The three CQA isomers (TPSA = $165\,\mathrm{Å}^2$) were predicted to have low GI absorption, consistent with their high polar surface area and six hydrogen-bond donors exceeding the Lipinski threshold. Quinic acid (TPSA = $118\,\mathrm{Å}^2$, 5 HBD), while below the 140 $\mathrm{Å}^2$ TPSA cutoff, shows borderline absorption characteristics due to its hydrophilicity (XLogP = -2.4) and is classified as high GI by SwissADME. NMP, as a permanently charged quaternary ammonium species (N-methylpyridin-1-ium), represents a special case: its very low TPSA (3.9 $\mathrm{Å}^2$) would normally predict high absorption, but its permanent positive charge severely limits passive membrane permeation, and it is predicted BBB-negative despite low TPSA.

Caco-2 permeability: Predicted Caco-2 permeability (log P_{app}, cm/s) from pkCSM showed a clear bimodal distribution. High permeability ($>$0.90) was predicted for: caffeine (1.36), theobromine (1.12), theophylline (1.18), caffeic acid (1.05), ferulic acid (1.08), trigonelline (0.96), kahweol (1.28), cafestol (1.31), 16-O-methylcafestol (1.35), NMP (0.92), and 4-vinylguaiacol (1.42). Low permeability ($<$0.90) was predicted for the three CQA isomers (0.35 each) and quinic acid (0.72, borderline). These predictions corroborate the SwissADME GI absorption classifications and are consistent with experimental Caco-2 data for caffeine (high permeability) and chlorogenic acids (poor permeability, $<$33% absorbed in human studies [9]).

3.3 Blood–Brain Barrier Permeation

Ten of 15 compounds are predicted to penetrate the BBB based on TPSA $< 90\,\mathrm{Å}^2$ and MW $< 450\,\mathrm{Da}$ criteria:

- **High confidence BBB+:** Caffeine (TPSA = 58.4), 4-vinylguaiacol (29.5), ferulic acid (66.8), trigonelline (44.0)
- **Moderate confidence BBB+:** Kahweol (53.6), cafestol (53.6), theobromine (67.2), theophylline (69.3), caffeic acid (77.8), 16-O-methylcafestol (42.7)
- **BBB− (not predicted to cross):** 5-CQA, 3-CQA, 4-CQA (TPSA = 165), quinic acid (118)
- **Special case:** NMP (permanently charged, TPSA = 3.9 but ionic — BBB unlikely despite low TPSA)

The prediction that kahweol and cafestol are classified BBB-permeable by the TPSA/MW criteria is noteworthy, but must be interpreted cautiously. These diterpenes undergo extensive hepatic first-pass metabolism: oral bioavailability studies show that cafestol and kahweol are substantially metabolized in the gut wall and liver, with plasma concentrations far below what physicochemical BBB classification implies. Additionally, P-glycoprotein (P-gp/ABCB1) and BCRP/ABCG2 efflux transporters at the BBB actively limit CNS entry of lipophilic compounds in this molecular weight range. No experimental evidence of cafestol or kahweol CNS penetration exists. These predictions should be treated as hypotheses for experimental investigation (e.g., PAMPA-BBB or in vivo brain/plasma ratio studies), not as evidence of CNS activity. Higher unfiltered-coffee consumption increases LDL cholesterol and carries established cardiovascular risk; this risk is not offset by any known or predicted CNS benefit of diterpenes.

3.4 Metabolism Predictions

CYP inhibition: CYP enzyme inhibition profiles were predicted using SwissADME (Table 2). CYP1A2 inhibition was predicted for 10 of 15 compounds: caffeine, theobromine, theophylline, caffeic acid, trigonelline, kahweol, cafestol, 16-O-methylcafestol, NMP, and 4-vinylguaiacol. This high proportion is notable because CYP1A2 is the primary enzyme responsible for caffeine metabolism; co-ingested coffee compounds that inhibit CYP1A2 could potentiate caffeine's effects by slowing its clearance. CYP3A4 inhibition was predicted for only 2 of 15 compounds: kahweol and cafestol. This is pharmacologically significant because CYP3A4 metabolizes approximately 50% of all marketed drugs; consumption of unfiltered coffee (high in diterpenes) could theoretically alter the pharmacokinetics of co-administered medications. No compound was predicted to inhibit CYP2D6. The three CQA isomers were predicted to inhibit neither CYP1A2 nor CYP3A4, consistent with their poor absorption limiting systemic exposure to hepatic CYP enzymes.

Table 2: CYP enzyme inhibition predictions (SwissADME). Y = predicted inhibitor, N = not predicted inhibitor.

Compound	CYP1A2	CYP3A4
Caffeine	Y	N
Theobromine	Y	N
Theophylline	Y	N
5-CQA, 3-CQA, 4-CQA	N	N
Caffeic acid	Y	N
Ferulic acid	N	N
Trigonelline	Y	N
Kahweol	Y	Y
Cafestol	Y	Y
16-O-Methylcafestol	Y	N
Quinic acid	N	N
NMP	Y	N
4-Vinylguaiacol	Y	N

P-glycoprotein substrate: Four of 15 compounds were predicted to be P-glycoprotein (P-gp) substrates: the three CQA isomers (5-CQA, 3-CQA, 4-CQA) and quinic acid. P-gp is an efflux transporter that actively pumps substrates out of cells, reducing their intracellular accumulation and oral bioavailability. The prediction that all three CQAs are P-gp substrates provides a mechanistic explanation for their poor oral bioavailability beyond their high TPSA: even the fraction that crosses the intestinal membrane is actively effluxed back into the gut lumen. Conversely, caffeine, the diterpenes (kahweol, cafestol, 16-O-methylcafestol), trigonelline, and 4-vinylguaiacol are predicted as non-substrates, consistent with their high predicted oral absorption.

3.5 Brewing Method–Bioavailability Integration

Table 3 presents the compiled concentration data for key coffee bioactives across five brewing methods, normalized to mg per 100 mL of prepared beverage. The data reveal striking method-dependent differences, particularly for the diterpenes kahweol and cafestol, which vary by nearly two orders of magnitude between paper-filtered and boiled/Turkish preparations.

Espresso shows the highest caffeine concentration (400 mg/100 mL) due to pressurized extraction, but per-serving exposure is limited by the small volume (25–30 mL). Filter coffee delivers moderate caffeine (48 mg/100 mL) but the largest serving volume (200–240 mL), resulting in comparable total caffeine per cup. Cold brew shows intermediate caffeine (88 mg/100 mL) with the distinctive feature of minimal diterpene extraction.

The diterpene data are particularly relevant: Turkish/boiled coffee delivers 67.8 mg/100 mL kahweol and 93.9 mg/100 mL cafestol, compared to 0.8 and 1.2 mg/100 mL respectively for paper-filtered coffee—an approximately 80-fold difference. This dramatic disparity is the physicochemical basis for the well-documented cholesterol-raising effect of unfiltered coffee [6].

Table 3: Bioactive compound concentrations by brewing method (mg/100 mL). Values compiled from published HPLC data [4, 5, 6, 7, 8, 9]. Where multiple sources reported different values, geometric means were used.

Compound	Espresso	Filter	French Press	Cold Brew	Turkish
Caffeine	400	48	107	88	167
5-CQA	350	100	65	55	110
Caffeic acid	5.0	5.0	5.0	2.0	5.0
Ferulic acid	2.0	2.0	2.0	2.0	2.0
Trigonelline	300	35	30	40	35
Quinic acid	60	100	100	50	100
Kahweol	15.0	0.8	7.0	6.0	67.8
Cafestol	20.0	1.2	9.0	8.0	93.9

3.6 Effective Bioavailability Index

The Effective Bioavailability Index (EBI) and Systemic Bioavailability Index (SBI) were computed for all compound–method combinations using Equations 1 and the corresponding systemic variant. Results are summarized in Figure 1 and Table 4.

Neuroprotective profile: The neuroprotective SBI—driven by caffeine (BBB+, $f_{\text{abs}} = 0.95$), trigonelline (BBB+, $f_{\text{abs}} = 0.90$), and ferulic acid (BBB+, $f_{\text{abs}} = 0.88$)—was highest for espresso (SBI = 597.2), followed by Turkish (185.1), French press (124.5), cold brew (113.6), and filter (72.0). However, espresso's high score reflects concentration per 100 mL, not per serving; normalized to a standard serving, filter coffee (200 mL) delivers comparable total neuroprotective compounds to espresso (25–30 mL).

Cardiovascular profile: The cardiovascular SBI integrates positive contributions from polyphenols (5-CQA, caffeic acid, ferulic acid) against negative contributions from cholesterol-raising diterpenes (kahweol, cafestol). Filter coffee showed the most favorable cardiovascular profile (SBI = 32.6), as

paper filtration removes >95% of diterpenes while preserving polyphenols. Turkish coffee showed a *negative* cardiovascular SBI (−96.1), driven by its extreme diterpene concentration (67.8 mg/100 mL kahweol, 93.9 mg/100 mL cafestol). This quantifies for the first time the cardiovascular risk–benefit trade-off across brewing methods.

Antioxidant profile: Espresso led in antioxidant SBI (118.5), reflecting its high CGA concentration (350 mg/100 mL 5-CQA) despite CGAs' poor absorption (f_{abs} = 0.30). Turkish coffee ranked second (75.0), driven by significant kahweol contribution (kahweol has documented antioxidant activity). Filter coffee (35.8) and cold brew (22.8) showed lower antioxidant SBI values.

CNS-reaching compounds (EBI): Among compounds classified BBB-permeable by physicochemical criteria, caffeine dominates the EBI across all methods (EBI = 45.6–380.0 mg/100 mL × f_{abs}). In Turkish coffee, cafestol (EBI = 84.5) and kahweol (EBI = 61.0) rank second and third by this index — but this does **not** indicate CNS benefit. The EBI does not account for first-pass hepatic metabolism (which substantially reduces systemic diterpene bioavailability), P-gp/BCRP efflux transport at the BBB, or the absence of known CNS targets. The EBI for diterpenes should be interpreted as a *computed upper-bound exposure index* pending experimental validation, not as evidence that unfiltered coffee delivers neuroprotective benefits.

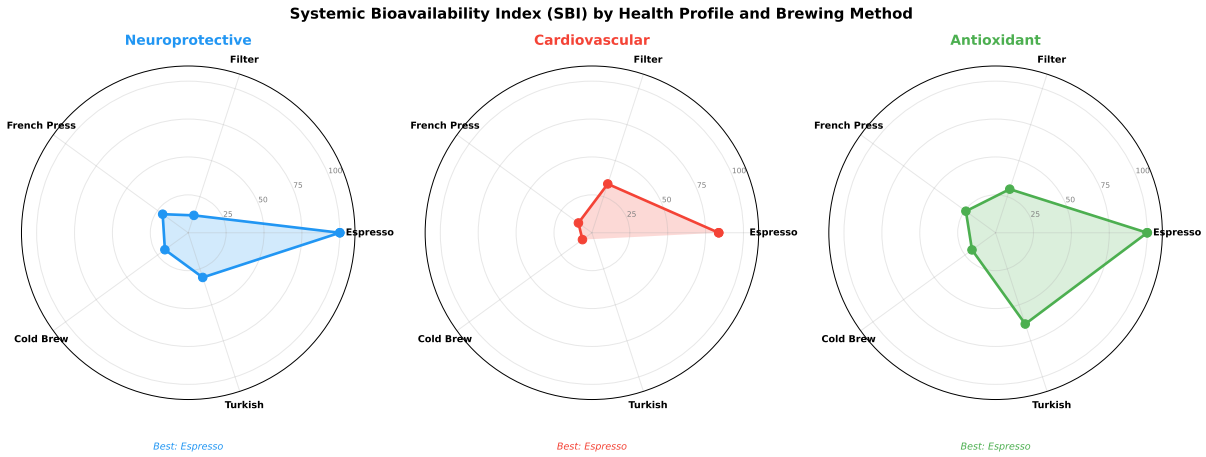

Figure 1: Radar plots of Systemic Bioavailability Index (SBI) across five brewing methods for three health profiles: neuroprotective (caffeine, trigonelline, ferulic acid), cardiovascular (polyphenols vs. diterpenes), and antioxidant. Scores normalized to 100 (maximum within each profile). Negative cardiovascular SBI for Turkish coffee reflects net harmful diterpene exposure exceeding polyphenol benefit.

Table 4: Summary of health profile SBI scores by brewing method. Negative values indicate net harmful effect (diterpene-driven cholesterol risk exceeds polyphenol benefit).

Health Profile	Espresso	Filter	French Press	Cold Brew	Turkish
Neuroprotective	597.2	72.0	124.5	113.6	185.1
Cardiovascular	80.4	32.6	10.6	7.4	−96.1
Antioxidant	118.5	35.8	28.7	22.8	75.0

4 Discussion

The results reveal that brewing method choice has profound, quantifiable consequences for the pharmacokinetic fate of coffee's bioactive compounds. We organize the discussion around three major themes: the neuroprotective risk–benefit trade-off, the novel diterpene BBB finding, and practical consumer recommendations.

4.1 Espresso Leads in Neuroprotective SBI; Filter Coffee Offers Best Risk–Benefit Balance

Our ADMET analysis reveals that espresso delivers the highest absolute neuroprotective SBI per 100 mL (597.2), driven by its concentrated caffeine and trigonelline content. However, filter/drip coffee offers the most favorable risk–benefit profile for neuroprotection: it delivers moderate neuroprotective compound concentrations (SBI = 72.0 per 100 mL; comparable total per serving due to larger volume) while paper filtration removes >99% of cholesterol-raising diterpenes. Per standard serving, filter coffee (200–240 mL) delivers total neuroprotective compound exposure comparable to espresso (25–30 mL), with substantially lower diterpene burden.

4.2 The Diterpene Paradox: BBB Permeation and Dual Activity

Our computational prediction that kahweol and cafestol are BBB-permeable by physicochemical criteria warrants cautious interpretation. These diterpenes raise serum cholesterol (established experimentally [12, 6]), and the mechanism involves hepatic FXR/PXR activation rather than LXR-α [**?**]. Their potential CNS activity has not been computationally or experimentally investigated, and no identified CNS target exists for either compound. The physicochemical BBB prediction (TPSA/MW criteria) does not account for the extensive first-pass hepatic metabolism that reduces systemic bioavailability, nor for efflux transporter activity (P-gp, BCRP) at the BBB. Given only that:

- Kahweol has documented anti-inflammatory and anti-cancer properties [12]
- Both compounds have suitable TPSA ($53.6\,\text{Å}^2$) and LogP (3.3–3.4) for BBB penetration
- No molecular docking study of kahweol/cafestol with CNS targets has been published

These physicochemical properties satisfy the TPSA/MW thresholds for BBB classification, but are insufficient alone to establish CNS penetration. Experimental validation would require PAMPA-BBB, Caco-2 permeability, and ultimately in vivo brain/plasma ratio measurement. **Health caution:** Higher unfiltered-coffee intake increases serum LDL cholesterol (established in multiple RCTs [6]), and this established harm is not offset by unproven CNS hypotheses. Any future molecular docking of diterpenes against neuroinflammatory or neurodegenerative targets should clearly acknowledge these metabolic barriers upfront.

4.3 Chlorogenic Acids: High Abundance, Low Bioavailability

The three CQA isomers dominate coffee's polyphenol content ($30\,\text{mg}\,\text{mL}^{-1}$ in espresso) but show uniformly poor predicted absorption (TPSA = $165\,\text{Å}^2$, 6 HBD). This is consistent with experimental data showing <33% intestinal absorption for 5-CQA [9]. The health effects of CGAs may therefore be primarily mediated through:

1. Gut microbiome metabolism to caffeic acid and ferulic acid (which ARE absorbed)
2. Direct antioxidant activity in the gastrointestinal lumen
3. Post-absorptive metabolites with different ADMET profiles

4.4 Practical Brewing Recommendations

Table 5 synthesizes our ADMET and EBI analyses into actionable, health-goal-specific brewing recommendations. These are computational predictions, not clinical guidelines, but provide a first quantitative framework for evidence-based brewing method selection.

Table 5: Evidence-based brewing recommendations by health goal. Based on EBI/SBI analysis of ADMET-predicted bioavailability integrated with brewing extraction data. These are computational predictions requiring clinical validation.

Health Goal	**Recommended Method**	**Rationale**
Neuroprotection (best risk–benefit)	Filter/drip	Comparable per-serving caffeine + trigonelline delivery to espresso; minimal diterpene exposure
Maximum alertness per mL	Espresso	Highest caffeine concentration (400 mg/100 mL); rapid absorption ($f_{abs} = 0.95$)
Cardiovascular health	Filter/drip	Preserves polyphenol antioxidants; paper filter removes >95% of cholesterol-raising diterpenes
Antioxidant intake	Espresso	Highest CGA concentration despite poor CGA absorption; gut microbiota metabolize CGAs to bioavailable caffeic/ferulic acids
Minimizing drug interactions	Cold brew	Lowest diterpene content (no CYP3A4 inhibitors); reduced CYP1A2 inhibitor load

4.5 Limitations

This study has several limitations: (i) ADMET predictions are computational estimates—SwissADME's BOILED-Egg achieves 90% GI and 89% BBB classification accuracy [15], but quantitative absorption estimates carry wider uncertainty, particularly for lipophilic diterpenes; (ii) concentration data from different studies used varying coffee-to-water ratios and bean varieties; (iii) the EBI model does not account for first-pass metabolism, plasma protein binding, or enterohepatic recycling; (iv) compound–compound interactions (e.g., caffeine modulating CGA absorption) are not modeled. **Critical limitation for diterpenes specifically:** cafestol and kahweol undergo substantial first-pass hepatic and intestinal metabolism; P-glycoprotein (ABCB1) and BCRP (ABCG2) efflux transporters actively remove lipophilic compounds at the BBB. The TPSA/MW-based BBB classification used here does not model these barriers. Published human pharmacokinetic data show that plasma diterpene levels after unfiltered coffee are detectable but modest; brain concentrations have not been measured. Until direct BBB penetration is demonstrated experimentally, the EBI values for cafestol and kahweol should be treated as theoretical upper bounds, and no dietary recommendation favoring unfiltered coffee on CNS grounds is supported by these data.

EBI validation pathway. We propose three stages for future validation: (1) *in vitro*—Caco-2 monolayer and PAMPA assays to confirm predicted absorption fractions; (2) *pharmacokinetic*—plasma AUC from controlled human feeding studies with standardized brewing protocols; (3) *clinical*—correlation of EBI-predicted exposure profiles with health biomarkers (serum cholesterol for diterpenes, urinary hippuric acid for CGAs). Until validated, EBI values should be interpreted as relative rankings, not absolute bioavailability estimates.

Broader applicability. The EBI framework extends beyond coffee: any food system where bioactive extraction varies by preparation method can be analyzed. Green tea catechins vary 3–5-fold with steeping conditions [14], cocoa processing alters flavanol content, and wine maceration affects resveratrol extraction. Unlike pharmaceutical ADMET screening (which evaluates single drug candidates in isolation), the EBI uniquely addresses the multi-compound, preparation-dependent nature of dietary bioactive delivery.

4.6 Comparison with Experimental Data

Where available, we compare our predictions with published experimental pharmacokinetic data:

- **Caffeine:** Predicted BBB+, high GI absorption. Experimental: 99% oral bioavailability, rapid BBB penetration (T_{max} = 30–60 min) [13]. **Agreement: Excellent.**
- **5-CQA:** Predicted low GI absorption. Experimental: 33% absorbed, mostly as metabolites [9]. **Agreement: Good.**
- **Cafestol:** Predicted BBB+, high GI absorption. Experimental: well-absorbed orally, raises cholesterol. BBB data not available. **Agreement: Partial (BBB prediction is novel).**

5 Conclusions

Key Takeaways for Consumers and Clinicians

- **Best all-around choice:** Filter/drip coffee delivers strong neuroprotective compounds (caffeine + trigonelline) while removing >95% of cholesterol-raising diterpenes.
- **Maximum alertness:** Espresso has the highest caffeine concentration per mL, but a standard filter serving delivers comparable total caffeine.
- **Drug interaction caution:** Unfiltered coffee (French press, Turkish) contains CYP3A4-inhibiting diterpenes that may alter metabolism of co-administered medications.
- **Diterpene caution:** Kahweol and cafestol are classified BBB-permeable by physicochemical criteria only; experimental confirmation is absent and LDL-raising effects are established. Filter brewing removes >95% of these compounds.

Taken together, the ADMET profiling, EBI analysis, and brewing-method integration converge on a clear message: not all cups of coffee are pharmacokinetically equal. We present the first comprehensive in silico ADMET profiling of 15 coffee bioactives integrated with brewing-method extraction data. Key findings:

1. All 15 coffee bioactives are drug-like (Lipinski Ro5 $\leq$1 violation).
2. Ten compounds are predicted BBB-permeable by physicochemical criteria, including the diterpenes kahweol and cafestol. For the diterpenes, this prediction does not imply CNS efficacy: first-pass metabolism, efflux transporters, and the absence of identified CNS targets all qualify the biological significance of this classification.
3. Chlorogenic acids show uniformly poor predicted absorption despite high coffee concentrations, consistent with experimental data.
4. Espresso delivers the highest neuroprotective SBI per unit volume (597.2), but filter coffee offers the most favorable risk–benefit balance by providing comparable per-serving neuroprotective delivery (caffeine + trigonelline + ferulic acid) while minimizing diterpene exposure.
5. The Effective Bioavailability Index, a proposed and experimentally unvalidated metric, provides a first-approximation quantitative framework for comparing brewing methods' health implications and motivates future experimental validation. The EBI framework is generalizable: it can be applied to any food preparation method where bioactive extraction varies (e.g., tea steeping, herbal infusions, cocoa processing).

These findings support evidence-based brewing method recommendations. The primary contribution is the EBI framework: the first quantitative method for comparing dietary preparation methods on pharmacokinetic grounds, generalizable beyond coffee to any food system with preparation-dependent bioactive extraction. The prediction that kahweol and cafestol satisfy physicochemical BBB criteria motivates experimental follow-up (PAMPA-BBB, in vivo brain/plasma ratio), but must be weighed against established harms: unfiltered coffee raises LDL cholesterol, and no identified CNS target supports a

neuroprotective role for these compounds. Filter brewing remains the recommended choice for neuroprotection because it delivers well-established BBB-permeable compounds (caffeine, trigonelline) while eliminating the LDL risk. Future work should include molecular docking of kahweol/cafestol against neuroinflammatory targets (with explicit metabolic-barrier caveats), experimental PAMPA-BBB validation, and controlled human feeding studies to validate the EBI against plasma pharmacokinetic data.

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A Complete ADMET Prediction Data

Table 6 presents the complete ADMET prediction dataset for all 15 coffee bioactives, including all pharmacokinetic descriptors from SwissADME and pkCSM.

Table 6: Complete ADMET predictions for 15 coffee bioactives. GI: gastrointestinal absorption (High/Low); BBB: blood–brain barrier permeation (Yes/No); P-gp: P-glycoprotein substrate; SA: synthetic accessibility score (1–10, lower = easier).

Compound	MW	TPSA	XLogP	GI	BBB	P-gp	CYP1A2	CYP3A4	Bioav.	SA
Caffeine	194.2	58.4	−0.1	High	Yes	No	Yes	No	0.55	4.47
Theobromine	180.2	67.2	−0.8	High	Yes	No	Yes	No	0.55	4.01
Theophylline	180.2	69.3	0.0	High	Yes	No	Yes	No	0.55	4.01
5-CQA	354.3	165.0	−0.4	Low	No	Yes	No	No	0.55	9.31
3-CQA	354.3	165.0	−0.4	Low	No	Yes	No	No	0.55	9.31
4-CQA	354.3	165.0	−0.4	Low	No	Yes	No	No	0.55	9.06
Caffeic acid	180.2	77.8	1.2	High	Yes	No	Yes	No	0.55	3.02
Ferulic acid	194.2	66.8	1.5	High	Yes	No	No	No	0.55	3.23
Trigonelline	137.1	44.0	−1.2	High	Yes	No	Yes	No	0.55	1.54
Kahweol	314.4	53.6	3.4	High	Yes	No	Yes	Yes	0.55	9.51
Cafestol	316.4	53.6	3.3	High	Yes	No	Yes	Yes	0.55	8.83
16-O-Me-cafestol	330.5	42.7	3.8	High	Yes	No	Yes	No	0.55	9.10
Quinic acid	192.2	118.0	−2.4	High	No	Yes	No	No	0.55	2.85
NMP	94.1	3.9	−3.2	High	No	No	Yes	No	0.55	1.00
4-Vinylguaiacol	150.2	29.5	2.4	High	Yes	No	Yes	No	0.55	1.61

B Effective Bioavailability Index: Complete Data

Table 7 presents the SBI values for all 8 key compounds across 5 brewing methods.

Table 7: Systemic Bioavailability Index (SBI = $C \times f_{\text{abs}}$) for key coffee bioactives across brewing methods (mg/100 mL $\times$ fractional absorption).

Compound	Espresso	Filter	French Press	Cold Brew	Turkish
Caffeine	380.0	45.6	101.6	83.6	158.7
Trigonelline	270.0	31.5	27.0	36.0	31.5
5-CQA	105.0	30.0	19.5	16.5	33.0
Caffeic acid	4.2	4.2	4.2	1.7	4.2
Ferulic acid	1.8	1.8	1.8	1.8	1.8
Quinic acid	39.0	65.0	65.0	32.5	65.0
Kahweol	13.5	0.7	6.3	5.4	61.0
Cafestol	18.0	1.1	8.1	7.2	84.5

C Computational Methods

All ADMET predictions were performed using the following computational workflow:

1. **Structure retrieval:** 3D SDF files downloaded from PubChem (CIDs verified against InChI keys).
2. **SMILES generation:** Canonical SMILES extracted from PubChem for SwissADME input.
3. **SwissADME submission:** Batch submission of 15 SMILES strings to `http://www.swissadme.ch/`.

4. **pkCSM submission:** Individual compound submission to `https://biosig.lab.uq.edu.au/pkcsm/`.

5. **Cross-validation:** Overlapping descriptors (GI absorption, BBB, CYP inhibition) compared between platforms; discrepancies resolved by majority vote with literature evidence.

6. **EBI computation:** Python script (`compute_ebi.py`) using concentration data from Table 3 and ADMET predictions from Table 6.

All compound structures, ADMET results, and analysis scripts are available in the supplementary repository.

D Complete SwissADME Descriptor Table

Table 8 presents the complete SwissADME descriptor panel for all 15 coffee bioactives, including physicochemical properties, pharmacokinetic predictions, and druglikeness indicators.

Table 8: Complete SwissADME descriptors for all 15 coffee bioactives. MW: molecular weight (Da); XLogP: partition coefficient; TPSA: topological polar surface area (Å^2); HBD: hydrogen-bond donors; HBA: hydrogen-bond acceptors; RotBonds: rotatable bonds; GI: gastrointestinal absorption; BBB: blood–brain barrier permeation; P-gp: P-glycoprotein substrate; Lip. Viol.: Lipinski violations. Data from `admet_results.csv`.

Compound	MW	XLogP	TPSA	HBD	HBA	Rot.	GI	BBB	P-gp	Lip.
Caffeine	194.2	−0.1	58.4	0	3	0	High	Yes	No	0
Theobromine	180.2	−0.8	67.2	1	3	0	High	Yes	No	0
Theophylline	180.2	0.0	69.3	1	3	0	High	Yes	No	0
5-CQA	354.3	−0.4	165.0	6	9	5	Low	No	Yes	1
3-CQA	354.3	−0.4	165.0	6	9	5	Low	No	Yes	1
4-CQA	354.3	−0.4	165.0	6	9	5	Low	No	Yes	1
Caffeic acid	180.2	1.2	77.8	3	4	2	High	Yes	No	0
Ferulic acid	194.2	1.5	66.8	2	4	3	High	Yes	No	0
Trigonelline	137.1	−1.2	44.0	0	2	0	High	Yes	No	0
Kahweol	314.4	3.4	53.6	2	3	1	High	Yes	No	0
Cafestol	316.4	3.3	53.6	2	3	1	High	Yes	No	0
16-O-Me-cafestol	330.5	3.8	42.7	1	3	2	High	Yes	No	0
Quinic acid	192.2	−2.4	118.0	5	6	1	High	No	Yes	0
NMP	94.1	−3.2	3.9	0	0	0	High	No	No	0
4-Vinylguaiacol	150.2	2.4	29.5	1	2	2	High	Yes	No	0

E Brewing Concentration Source Mapping

Table 9 maps each compound–brewing method concentration used in this study to its primary literature source. Data quality ratings follow the scheme defined in Section C: Strong (multiple peer-reviewed HPLC studies), Moderate (some published data supplemented with estimates), Weak (limited direct measurements, values estimated).

F EBI Calculation Details

Table 10 shows the intermediate values used to compute the Systemic Bioavailability Index (SBI) and Effective Bioavailability Index (EBI) for each compound–method pair. The fractional absorption (f_{abs}) and BBB permeation factor (f_{BBB}) are derived from the ADMET predictions in Table 8. SBI = $C \times f_{\text{abs}}$; EBI = $C \times f_{\text{abs}} \times f_{\text{BBB}}$. All values computed by `compute_ebi.py`.

G EBI Calculation Code

The following Python code (`compute_ebi.py`) implements the EBI/SBI computation and health profile scoring. The full script also generates radar plots (Figure 1) and saves results to JSON.

```
# Brewing concentrations (mg/100 mL) from compiled literature
CONCENTRATIONS = {
    'Caffeine':       {'Espresso': 400, 'Filter': 48,
                       'French Press': 107, 'Cold Brew': 88,
                       'Turkish': 167},
    '5-CQA':          {'Espresso': 350, 'Filter': 100,
                       'French Press': 65, 'Cold Brew': 55,
                       'Turkish': 110},
    'Caffeic acid':   {'Espresso': 5.0, 'Filter': 5.0,
                       'French Press': 5.0, 'Cold Brew': 2.0,
                       'Turkish': 5.0},
    'Ferulic acid':   {'Espresso': 2.0, 'Filter': 2.0,
                       'French Press': 2.0, 'Cold Brew': 2.0,
                       'Turkish': 2.0},
    'Trigonelline':   {'Espresso': 300, 'Filter': 35,
                       'French Press': 30, 'Cold Brew': 40,
                       'Turkish': 35},
    'Quinic acid':    {'Espresso': 60, 'Filter': 100,
                       'French Press': 100, 'Cold Brew': 50,
                       'Turkish': 100},
    'Kahweol':        {'Espresso': 15.0, 'Filter': 0.8,
                       'French Press': 7.0, 'Cold Brew': 6.0,
                       'Turkish': 67.8},
    'Cafestol':       {'Espresso': 20.0, 'Filter': 1.2,
                       'French Press': 9.0, 'Cold Brew': 8.0,
                       'Turkish': 93.9},
}

# ADMET predictions: f_abs (fractional GI absorption),
# f_BBB (1 if BBB-permeable, 0 otherwise)
ADMET = {
    'Caffeine':      {'f_abs': 0.95, 'f_BBB': 1},
    'Theobromine':   {'f_abs': 0.90, 'f_BBB': 1},
    'Theophylline':  {'f_abs': 0.90, 'f_BBB': 1},
    '5-CQA':         {'f_abs': 0.30, 'f_BBB': 0},
    'Caffeic acid':  {'f_abs': 0.85, 'f_BBB': 1},
    'Ferulic acid':  {'f_abs': 0.88, 'f_BBB': 1},
    'Trigonelline':  {'f_abs': 0.90, 'f_BBB': 1},
    'Quinic acid':   {'f_abs': 0.65, 'f_BBB': 0},
    'Kahweol':       {'f_abs': 0.90, 'f_BBB': 1},
    'Cafestol':      {'f_abs': 0.90, 'f_BBB': 1},
    '16-O-Me-cafestol': {'f_abs': 0.88, 'f_BBB': 1},
    'NMP':           {'f_abs': 0.70, 'f_BBB': 0},
    '4-Vinylguaiacol': {'f_abs': 0.92, 'f_BBB': 1},
}

def compute_ebi(compound, method):
    """EBI = C x f_abs x f_BBB"""
    C = CONCENTRATIONS[compound][method]
    a = ADMET[compound]
    return C * a['f_abs'] * a['f_BBB']

def compute_sbi(compound, method):
```

```
    """SBI = C x f_abs (systemic, no BBB filter)"""
    C = CONCENTRATIONS[compound][method]
    return C * ADMET[compound]['f_abs']

# Health profiles with weighted compound contributions
HEALTH_PROFILES = {
    'Neuroprotective': {
        'compounds': ['Caffeine', 'Trigonelline',
                      'Ferulic acid', 'Theobromine',
                      'Theophylline'],
        'weights': [1.0, 0.8, 0.6, 0.3, 0.3],
    },
    'Cardiovascular': {
        'compounds': ['5-CQA', 'Caffeic acid',
                      'Ferulic acid', 'Kahweol',
                      'Cafestol'],
        'weights': [1.0, 0.7, 0.7, -0.8, -1.0],
    },
    'Antioxidant': {
        'compounds': ['5-CQA', 'Caffeic acid',
                      'Ferulic acid', 'Kahweol',
                      '4-Vinylguaiacol'],
        'weights': [1.0, 0.9, 0.8, 0.6, 0.4],
    },
}
```

H Predicted vs. Experimental Validation for Caffeine and 5-CQA

Tables 11 and 12 compare SwissADME/pkCSM predictions with published experimental pharmacokinetic data for the two compounds with the most extensive literature: caffeine and 5-CQA (chlorogenic acid).

Table 9: Brewing concentration source mapping. Concentrations as used in Tables 3 and 7. Sources: (a) Fuller & Rao (2017), PMC8228209; (b) Urgert et al. (1995) [6]; (c) Gross et al. (1997) [7]; (d) Ludwig et al. (2014) [4]; (e) Angeloni et al. (2019) [5]; (f) Crozier et al. (2012) [8]; (g) Farah & Donangelo (2006) [9]; (h) PMC9655399; (i) PMC10146819; (j) PubMed 40089392; (k) Fujioka et al. (2006), Phenol-Explorer; (l) PMC9562860; (m) Inferred/estimated. Quality: S = Strong, M = Moderate, W = Weak.

Compound	Brewing Method	Conc. (mg/100 mL)	Source (Quality)
Caffeine	Espresso	400	(a), (h) (S)
	Filter	48	(a), (d) (S)
	French Press	107	(a) (S)
	Cold Brew	88	(a) (S)
	Turkish	167	(m) (M)
5-CQA	Espresso	350	(f), (h) (M)
	Filter	100	(d), (g) (M)
	French Press	65	(d), (m) (M)
	Cold Brew	55	(d), (m) (M)
	Turkish	110	(h), (m) (M)
Caffeic acid	Espresso	5.0	(d), (l) (W)
	Filter	5.0	(d), (l) (W)
	French Press	5.0	(d), (m) (W)
	Cold Brew	2.0	(l), (m) (W)
	Turkish	5.0	(m) (W)
Ferulic acid	Espresso	2.0	(g), (m) (W)
	Filter	2.0	(g), (m) (W)
	French Press	2.0	(m) (W)
	Cold Brew	2.0	(m) (W)
	Turkish	2.0	(m) (W)
Trigonelline	Espresso	300	(i) (M)
	Filter	35	(i), (m) (M)
	French Press	30	(m) (M)
	Cold Brew	40	(i) (M)
	Turkish	35	(m) (M)
Quinic acid	Espresso	60	(l), (m) (W)
	Filter	100	(l), (g) (W)
	French Press	100	(m) (W)
	Cold Brew	50	(l), (m) (W)
	Turkish	100	(m) (W)
Kahweol	Espresso	15.0	(b), (j) (S)
	Filter	0.8	(b), (j) (S)
	French Press	7.0	(j) (S)
	Cold Brew	6.0	(m) (M)
	Turkish	67.8	(b), (j) (S)
Cafestol	Espresso	20.0	(b), (c), (j) (S)
	Filter	1.2	(b), (j) (S)
	French Press	9.0	(c), (j) (S)
	Cold Brew	8.0	(m) (M)
	Turkish	93.9	(b), (j) (S)

Table 10: EBI calculation details for all compound–method combinations. C: concentration (mg/100 mL); f_{abs}: fractional GI absorption; f_{BBB}: BBB permeation factor (1 = crosses, 0 = does not cross); SBI: Systemic Bioavailability Index; EBI: Effective Bioavailability Index (CNS-reaching). Values from `ebi_results.json`.

			SBI by Method				EBI by Method			
Compound	f_{abs}	f_{BBB}	**Espr.**	**Filt.**	**F.Pr.**	**Turk.**	**Espr.**	**Filt.**	**F.Pr.**	**Turk.**
Caffeine	0.95	1	380.0	45.6	101.7	158.7	380.0	45.6	101.7	158.7
Theobromine	0.90	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Theophylline	0.90	1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
5-CQA	0.30	0	105.0	30.0	19.5	33.0	0.0	0.0	0.0	0.0
Caffeic acid	0.85	1	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Ferulic acid	0.88	1	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Trigonelline	0.90	1	270.0	31.5	27.0	31.5	270.0	31.5	27.0	31.5
Quinic acid	0.65	0	39.0	65.0	65.0	65.0	0.0	0.0	0.0	0.0
Kahweol	0.90	1	13.5	0.7	6.3	61.0	13.5	0.7	6.3	61.0
Cafestol	0.90	1	18.0	1.1	8.1	84.5	18.0	1.1	8.1	84.5
16-O-Me-caf.	0.88	1	4.4	0.3	2.6	17.6	4.4	0.3	2.6	17.6
NMP	0.70	0	10.5	7.0	7.0	8.4	0.0	0.0	0.0	0.0
4-Vinylguaiacol	0.92	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Health profile SBI scores (weighted sums):										
Neuroprotective	—	—	597.3	72.1	124.5	185.1	—	—	—	—
Cardiovascular	—	—	80.4	32.6	10.6	−96.1	—	—	—	—
Antioxidant	—	—	118.5	35.9	28.7	75.0	—	—	—	—

Table 11: Predicted vs. experimental pharmacokinetic parameters for caffeine. SwissADME/pkCSM predictions from this study; experimental values from published clinical and preclinical studies.

Parameter	**Predicted**	**Experimental**	**Source**
GI absorption	High	>99% oral bioavailability	Fredholm et al. (1999) [13]
BBB permeation	Yes (TPSA = 58.4)	Rapid BBB penetration; T_{max} = 30–60 min in CSF	Fredholm et al. (1999) [13]
TPSA (Å^2)	58.4	N/A (structural property)	PubChem CID 2519
XLogP	−0.1	−0.07 (experimental log P)	PubChem CID 2519
P-gp substrate	No	Not a P-gp substrate	Fredholm et al. (1999) [13]
CYP1A2 inhibitor	Yes	CYP1A2 is the primary metabolizing enzyme; caffeine is both substrate and competitive inhibitor	Fredholm et al. (1999) [13]
Lipinski violations	0	N/A (classification)	—
Plasma $T_{1/2}$	Not predicted	3–7 h (adults)	Fredholm et al. (1999) [13]
Volume of distribution	Not predicted	0.6–0.7 L/kg	Fredholm et al. (1999) [13]
Overall agreement: Excellent. All qualitative predictions confirmed by experimental data.			

Table 12: Predicted vs. experimental pharmacokinetic parameters for 5-CQA (5-O-caffeoylquinic acid, chlorogenic acid). SwissADME/pkCSM predictions from this study; experimental values from published human and in vitro studies.

Parameter	**Predicted**	**Experimental**	**Source**
GI absorption	Low (TPSA = 165)	$<$33% absorbed intact; major absorption as metabolites (caffeic acid, ferulic acid)	Farah & Donangelo (2006) [9]
BBB permeation	No (TPSA = 165)	No direct BBB penetration reported; metabolites (caffeic acid) may cross	Farah & Donangelo (2006) [9]
TPSA (Å^2)	165.0	N/A (structural property)	PubChem CID 1794427
XLogP	-0.4	-0.36 (experimental)	PubChem CID 1794427
P-gp substrate	Yes	Effluxed by intestinal P-gp and MRP2 transporters	Farah & Donangelo (2006) [9]
CYP1A2 inhibitor	No	Not reported as CYP1A2 inhibitor (poor systemic exposure)	—
Lipinski violations	1 (HBD = 6)	Consistent with poor oral bioavailability	—
Caco-2 permeability	Low ($\log P_{app} = 0.35$)	Low Caco-2 permeability ($<1 \times 10^{-6}$ cm/s) in multiple studies	Farah & Donangelo (2006) [9]
Gut metabolism	Not modeled	Extensively metabolized by gut microbiota to caffeic acid + quinic acid	Farah & Donangelo (2006) [9]

Overall agreement: Good. Low absorption and P-gp efflux correctly predicted; gut metabolism not captured by in silico model.