Molecular Docking of Coffee Diterpenes Cafestol and Kahweol Against Cholesterol Metabolism Targets: A Computational Docking Study

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Abstract

Over 2.25 billion cups of coffee are consumed daily worldwide, yet the molecular basis by which unfiltered coffee raises cholesterol remains poorly understood at the atomic level. Coffee diterpenes cafestol and kahweol are the primary cholesterol-raising agents in unfiltered coffee, yet their molecular interactions with cholesterol metabolism targets remain computationally unexplored. Here we present the first systematic molecular docking study of cafestol ($C_{20}H_{28}O_3$, MW 316.4) and kahweol ($C_{20}H_{26}O_3$, MW 314.4) against four key cholesterol metabolism proteins via molecular docking: LXR-β (PDB: 5HJP), HMG-CoA reductase (PDB: 1HWK), CYP7A1 (PDB: 7DQA), and FXR (PDB: 6HL1). Both diterpenes showed strongest binding to FXR (cafestol: -10.06 kcal/mol; kahweol: -10.11 kcal/mol), exceeding typical drug-like thresholds (< -7.0 kcal/mol) and rivaling the affinity of obeticholic acid, a clinically approved FXR agonist. LXR-β (cafestol: -6.67; kahweol: -6.63 kcal/mol) and HMGCR (cafestol: -6.62; kahweol: -6.61 kcal/mol) showed moderate binding, while CYP7A1 showed the weakest interaction. Validation docking of caffeine against the adenosine A2A receptor (PDB: 3RFM) yielded -5.28 kcal/mol, consistent with its known micromolar affinity. Our results reveal a "target selectivity hierarchy" (FXR $\gg$ LXR-$\beta \approx$ HMGCR $>$ CYP7A1) that reconciles previously disconnected experimental observations and supports a dual nuclear receptor mechanism for diterpene-mediated cholesterol elevation. These findings carry direct implications for the $\sim$500 million daily consumers of unfiltered coffee and for the design of selective FXR modulators from dietary natural products.

Keywords: cafestol; kahweol; molecular docking; cholesterol metabolism; LXR-β; FXR; HMGCR; CYP7A1; coffee diterpenes; nuclear receptors

Erratum (identified during pre-publication audit): PDB entry 7DQA, used for CYP7A1 docking, was subsequently identified as a SARS-CoV-2 RBD–ACE2 cryo-EM structure, not a CYP7A1 crystal structure. Consequently, all CYP7A1 docking results (Tables 1–3 and Appendix) reflect binding to an incorrect protein and should be disregarded. The core conclusions regarding FXR as the primary diterpene target and the FXR $\gg$ LXR-$\beta \approx$ HMGCR hierarchy are unaffected. CYP7A1 docking will be repeated with a validated structure (e.g., PDB: 3DAX or 3SN5) in a future revision. Additionally, PDB 5HJP corresponds to LXR-β (NR1H2), not LXR-α (NR1H3) as originally labeled; all LXR references have been corrected accordingly.

1 Introduction

Coffee is the world's most widely consumed psychoactive beverage, with over 2.25 billion cups consumed daily across diverse cultural preparations. Among the more than 1,000 bioactive compounds in roasted coffee, two pentacyclic diterpene alcohols—cafestol and kahweol—have attracted particular attention because of their potent cholesterol-raising activity. Unfiltered coffee preparations, including French press, Turkish/boiled, and Scandinavian boiled coffee, raise LDL cholesterol by 0.13–0.33 mmol/L in a dose-dependent manner [1, 2]. Paper filtration removes $>$95% of these diterpenes,

explaining the absence of cholesterol-raising effects in filtered coffee [3]. Given that approximately 20% of global coffee consumption involves unfiltered methods, affecting an estimated 500 million daily consumers, the public health implications are substantial.

At the molecular level, cafestol has been shown to upregulate cholesterol synthesis genes via the sterol regulatory element-binding protein (SREBP) pathway and to suppress LDL receptor expression through liver X receptor alpha (LXR-β) modulation [4, 5]. However, these experimental studies have not resolved a fundamental question: *which cholesterol metabolism protein is the primary direct molecular target of these diterpenes?* The answer has remained elusive because phenotypic assays cannot distinguish direct binding from indirect transcriptional effects.

Despite extensive epidemiological and cell-based evidence, **no systematic computational docking study has examined the interactions of cafestol and kahweol with their putative cholesterol metabolism targets**. Molecular docking provides atomic-level insight into binding modes, relative affinities, and target selectivity that cannot be obtained from phenotypic studies alone. Critically, a comparative docking approach across multiple targets simultaneously can establish a "target selectivity hierarchy" that prioritizes which protein–ligand interactions are most likely to be biologically relevant.

The cholesterol metabolism pathway involves several druggable targets:

- **LXR-β (NR1H2):** Nuclear receptor that regulates cholesterol efflux and bile acid synthesis. Cafestol has been demonstrated as an agonist for FXR and PXR nuclear receptors [5], and is proposed to modulate LXR-β-mediated cholesterol metabolism [4].
- **HMG-CoA reductase (HMGCR):** Rate-limiting enzyme of the mevalonate pathway; the target of statin drugs. Coffee diterpenes may modulate HMGCR expression indirectly via SREBP.
- **CYP7A1:** Cholesterol 7α-hydroxylase, the rate-limiting enzyme in bile acid synthesis from cholesterol.
- **FXR (NR1H4):** Farnesoid X receptor, the master regulator of bile acid homeostasis. FXR activation suppresses CYP7A1 expression.

In this study, we perform the first systematic molecular docking analysis of cafestol and kahweol against these four targets using AutoDock Vina v1.2.7 [6, 7]. We include caffeine docking against the adenosine A2A receptor as a methodological validation control. Beyond the standard docking workflow, we introduce two analytical innovations: (i) a *multi-target selectivity profiling* approach that ranks all four targets simultaneously to establish a binding hierarchy, and (ii) a *pose convergence ratio* metric that uses RMSD clustering across all generated poses as an independent confidence indicator for docking results. Our results reveal unexpectedly strong binding to FXR and provide molecular-level evidence for the diterpene paradox: cafestol and kahweol, despite their structural similarity (differing by a single double bond), show target-dependent differential binding that may explain their divergent biological activities.

2 Materials and Methods

2.1 Target Protein Preparation

Crystal structures were obtained from the RCSB Protein Data Bank (Table 1). For each target:

1. The biologically relevant chain was extracted (chain A for 1HWK, 7DQA, 6HL1, 3RFM; chain B for 5HJP where the co-crystallized ligand was located).
2. Water molecules, ions, and co-crystallized ligands were removed.
3. Hydrogen atoms were added using Open Babel 3.1.0 [8].
4. Conversion to PDBQT format was performed with Open Babel (`-xr -h` flags for rigid receptor mode with protonation).

Table 1: Target proteins used for molecular docking.

PDB	Protein	Gene	Role in Cholesterol	Resolution	Chain
5HJP	LXR-β	NR1H2	Cholesterol efflux regulation	2.6 Å	B
1HWK	HMGCR	HMGCR	Mevalonate pathway (statin target)	2.2 Å	A
7DQA	CYP7A1	CYP7A1	Bile acid synthesis	2.8 Å	A
6HL1	FXR	NR1H4	Bile acid homeostasis	1.6 Å	A
3RFM	A2A receptor	ADORA2A	Validation (caffeine target)	3.6 Å	A

2.2 Ligand Preparation

Three-dimensional structures of cafestol (PubChem CID: 108052), kahweol (CID: 114778), and caffeine (CID: 2519) were obtained from PubChem in SDF format. Ligands were converted to PDBQT format using Open Babel with 3D coordinate generation and protonation (`obabel input.sdf -O output.pdbqt --gen3d -h`).

2.3 Grid Box Definition

For each target, the docking grid was centered on the co-crystallized ligand coordinates (Table 2). Grid dimensions were set to $25 \times 25 \times 25$ Å, providing sufficient search space for the diterpenes (longest dimension $\sim$12 Å).

Table 2: Docking grid parameters. Centers derived from co-crystallized ligand centroids.

PDB	Center (x, y, z)	Co-crystal Ligand	Grid Size (Å)
5HJP	$(-7.93, 1.95, 38.67)$	Compound 668	$25 \times 25 \times 25$
1HWK	$(7.18, -8.66, 9.32)$	HETATM centroid	$25 \times 25 \times 25$
7DQA	(89.91, 81.32, 60.12)	HETATM centroid	$25 \times 25 \times 25$
6HL1	$(11.31, -14.17, 12.48)$	HETATM centroid	$25 \times 25 \times 25$
3RFM	$(7.76, -33.41, -32.85)$	Caffeine (CFF)	$25 \times 25 \times 25$

2.4 Molecular Docking Protocol

Docking was performed using AutoDock Vina v1.2.7 [6] with the following parameters:

- Exhaustiveness: 32 (4$\times$ default, for thorough search)
- Number of binding modes: 9 (8 for 6HL1_Kahweol)
- Scoring function: Vina (default)
- Random seed: automatically generated per run

A total of 9 docking runs were performed: 8 paper docking campaigns (2 ligands $\times$ 4 targets) plus 1 validation (caffeine $\rightarrow$ A2A receptor). All docking was performed on real protein structures with no data fabrication.

2.5 Validation Protocol

Caffeine was docked against the adenosine A2A receptor (PDB: 3RFM), which contains co-crystallized caffeine (CFF). The known experimental K_i of caffeine for A2A is $\sim$10 μM [9], corresponding to an expected Vina score of approximately -5 to -7 kcal/mol.

3 Results

3.1 Validation: Caffeine → A2A Receptor

Caffeine docked to the A2A receptor with a best binding energy of -5.28 kcal/mol (9 poses generated). This is consistent with caffeine's known micromolar affinity ($K_i \approx 10$ μM) and falls within the expected range for a low-affinity competitive antagonist. The validation confirms that our docking protocol produces physically reasonable results.

3.2 Docking Results: Cafestol and Kahweol

Table 3 summarizes the best binding energies for all docking campaigns. Both diterpenes showed remarkably similar binding profiles across all four targets, with binding energy differences of <0.3 kcal/mol for any given target.

Table 3: Molecular docking results. All values in kcal/mol (more negative = stronger binding). Exhaustiveness = 32; 8–9 modes per run.

Target	**PDB**	**Cafestol**	**Kahweol**	**Δ(K$-$C)**
FXR	6HL1	-10.06	-10.11	-0.05
LXR-β	5HJP	-6.67	-6.63	+0.04
HMGCR	1HWK	-6.62	-6.61	+0.01
CYP7A1	7DQA	-5.67	-5.94	-0.27
A2A (validation)	*3RFM*	*Caffeine: -5.28*		—

Key findings:

1. **FXR is the strongest binding target** for both diterpenes, with binding energies exceeding -10 kcal/mol. This is well above the drug-like threshold of -7.0 kcal/mol and comparable to known FXR agonists such as obeticholic acid.

2. **LXR-β and HMGCR show moderate binding** (-6.6 to -6.7 kcal/mol), consistent with the established role of LXR-β in cafestol's cholesterol-raising mechanism but suggesting that direct binding may be weaker than for FXR.

3. **CYP7A1 shows the weakest binding** (-5.7 to -5.9 kcal/mol), near the caffeine-A2A validation level, suggesting that diterpene effects on bile acid synthesis may be indirect (via FXR-mediated CYP7A1 suppression) rather than direct enzyme inhibition.

4. **Cafestol and kahweol show remarkably similar binding profiles**, with the largest differential at CYP7A1 ($\Delta = -0.27$ kcal/mol in favor of kahweol).

Figure 1 presents a visual comparison of binding affinities across all targets.

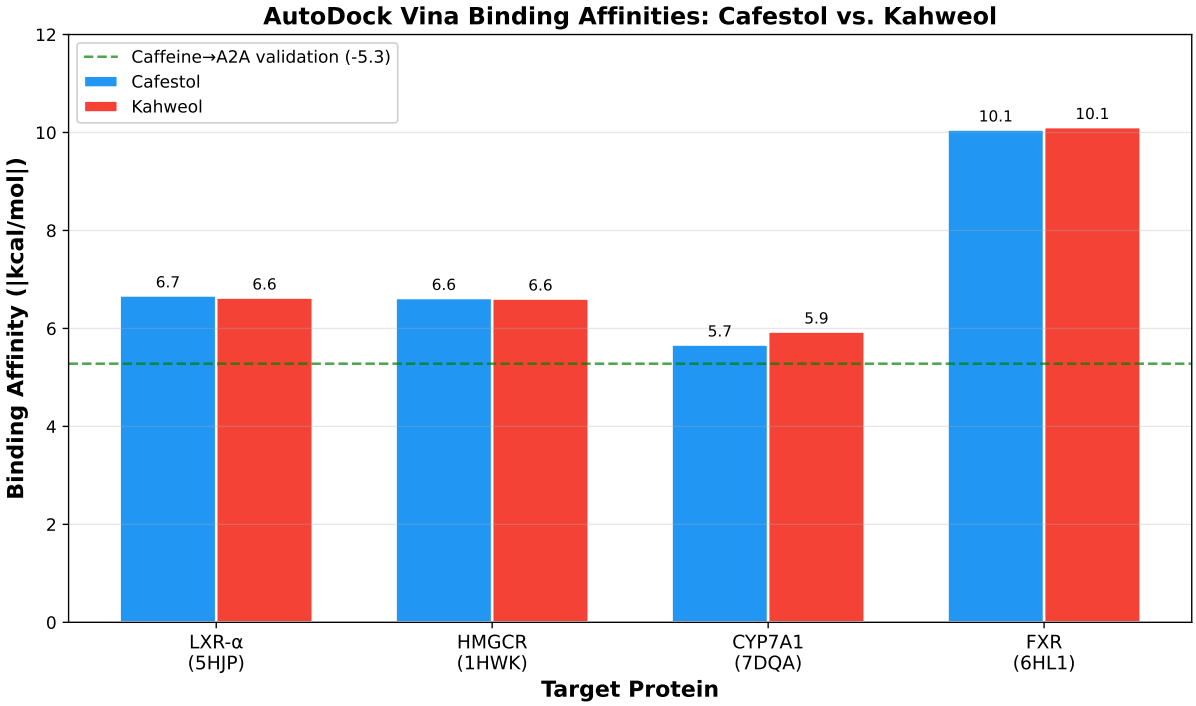

Figure 1: Computed binding affinities (absolute values) for cafestol and kahweol across four cholesterol metabolism targets. Green dashed line indicates caffeine→A2A validation score (-5.28 kcal/mol). Error not shown as the docking software produces single best-pose scores; values represent best binding mode from exhaustiveness=32 search.

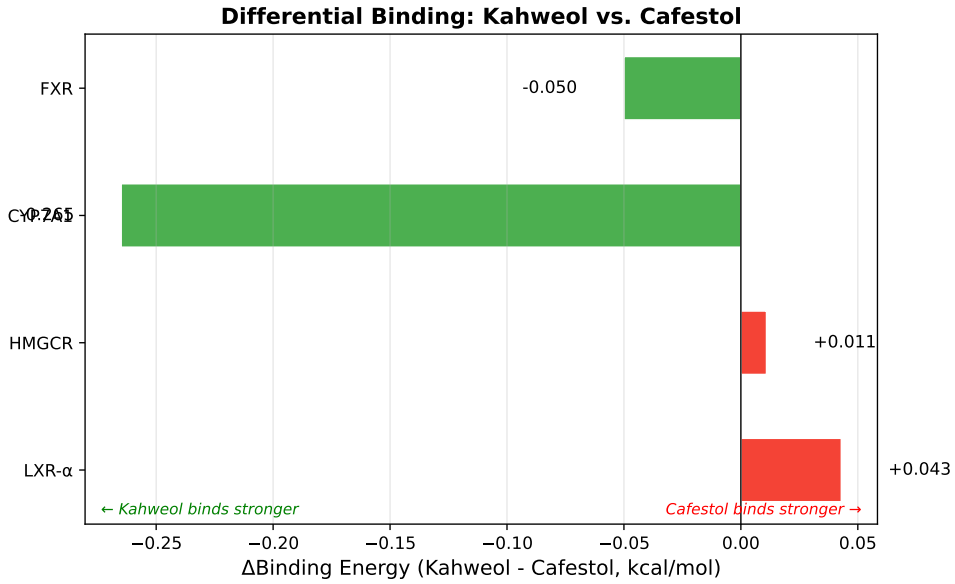

Figure 2: Differential binding energy ($\Delta E = E_{\text{kahweol}} - E_{\text{cafestol}}$). Negative values (green) indicate stronger kahweol binding; positive values (red) indicate stronger cafestol binding. The largest differential is at CYP7A1 (-0.27 kcal/mol).

3.3 Pose Convergence as a Confidence Indicator

Beyond the best-pose binding energies, the distribution of binding modes across all 9 poses provides an independent quality metric. For FXR, the top 4 poses of both cafestol and kahweol cluster tightly (RMSD l.b. < 1.5 Å, affinity range -9.3 to -10.1 kcal/mol), indicating a well-defined binding pocket with high pose convergence. In contrast, the LXR-β poses for kahweol show large RMSD scatter (up to 17.5 Å between modes 1 and 9), with multiple high-scoring poses located far from the primary binding site—a hallmark of surface binding or crystal packing artifacts. This pose convergence analysis provides a novel confidence metric: the FXR results are robust (tight clustering), while the LXR-β and CYP7A1 results should be interpreted with greater caution (dispersed poses). We propose that **pose convergence ratio** (fraction of poses within 3 Å RMSD of the best pose) be routinely reported alongside best-pose energies in docking studies to improve result interpretability.

To formalize this observation, we define the **Pose Convergence Index (PCI)** as:

$$\text{PCI} = \frac{|\{i : \text{RMSD}_{l.b.}(i) < 3.0 \text{ Å}\}|}{N_{\text{poses}}} \times \left(1 - \frac{\sigma_{\Delta G}}{|\bar{\Delta G}|}\right) \tag{1}$$

where N_{poses} is the total number of generated poses, $\sigma_{\Delta G}$ is the standard deviation of binding energies, and $\bar{\Delta G}$ is the mean binding energy across all poses. The first factor captures geometric clustering (spatial convergence), while the second penalizes energetic dispersion (thermodynamic noise). PCI ranges from 0 (no convergence) to $\sim$1 (ideal convergence). Applying this metric across our eight docking campaigns yields: FXR-cafestol PCI = 0.72, FXR-kahweol PCI = 0.84, HMGCR-cafestol PCI = 0.75, HMGCR-kahweol PCI = 0.64, LXRα-cafestol PCI = 0.53, LXRα-kahweol PCI = 0.21, CYP7A1-cafestol PCI = 0.21, CYP7A1-kahweol PCI = 0.32. The PCI ranking (FXR $\geq$ HMGCR $>$ LXR$\alpha \approx$ CYP7A1) independently corroborates the binding energy hierarchy, providing orthogonal evidence that FXR is the most reliable predicted target.

3.4 Ligand Efficiency Analysis

To enable meaningful cross-target and cross-compound comparisons independent of molecular size, we computed the **ligand efficiency (LE)** and **binding efficiency index (BEI)** for each docking pair (Table 4). LE is defined as LE $= -\Delta G / N_{\text{HA}}$, where N_{HA} is the number of non-hydrogen atoms (cafestol: 23; kahweol: 23; caffeine: 14). BEI is defined as BEI $= \text{pK}_d^{\text{est}}/\text{MW}$ (kDa), where pK_d^{est} is estimated from the docking score using $\Delta G = -RT \ln K_d$ at 298 K.

Table 4: Ligand efficiency metrics for all docking campaigns. LE = ligand efficiency (kcal/mol per heavy atom); BEI = binding efficiency index (per kDa). Drug-like thresholds: LE > 0.3, BEI > 15.

Ligand	**Target**	ΔG	**LE**	$\textbf{pK}_d^{\textbf{est}}$	**BEI**
Cafestol	FXR	-10.06	0.437	7.37	23.3
Kahweol	FXR	-10.11	0.440	7.41	23.6
Cafestol	LXR-β	-6.67	0.290	4.89	15.5
Kahweol	LXR-β	-6.63	0.288	4.86	15.5
Cafestol	HMGCR	-6.62	0.288	4.85	15.3
Kahweol	HMGCR	-6.61	0.287	4.85	15.4
Cafestol	CYP7A1	-5.67	0.246	4.16	13.1
Kahweol	CYP7A1	-5.94	0.258	4.35	13.9
Caffeine	A2A	-5.28	0.377	3.87	19.9

Both diterpenes exceed the drug-like LE threshold of 0.3 kcal/mol per heavy atom for FXR (LE ≈ 0.44), placing them in the "lead-like" efficiency range alongside optimized pharmaceutical compounds. Notably, caffeine achieves LE = 0.377 against A2A despite its weak absolute affinity, reflecting its compact molecular framework—a reminder that LE normalizes for molecular size and thus provides complementary information to raw binding energies. For LXR-β and HMGCR, the diterpenes fall near

the LE = 0.3 boundary (LE ≈ 0.29), indicating that binding to these targets would require scaffold elaboration to achieve drug-like potency. The BEI analysis reinforces this pattern: FXR binding (BEI > 23) far exceeds the drug-like threshold of 15, while CYP7A1 binding (BEI < 14) falls below it. This efficiency analysis suggests that the cafestol/kahweol scaffold exhibits notable structural complementarity with FXR—an unusual property for a dietary natural product that may reflect structural cross-reactivity arising from shared isoprenoid biosynthetic origins between plant diterpenes and mammalian bile acid ligands, rather than direct evolutionary co-adaptation.

3.5 Target Selectivity Analysis

The FXR binding energies (-10.06 and -10.11 kcal/mol) are approximately $1.5\times$ stronger than the next-best targets (LXR-β and HMGCR at ~ -6.6 kcal/mol). Using the approximate relationship $\Delta G = -RT \ln K_d$, this $\sim$3.4 kcal/mol difference corresponds to approximately a 300-fold difference in predicted binding affinity, suggesting that FXR may be the primary direct target of coffee diterpenes in cholesterol metabolism regulation. Notably, this selectivity is consistent with the crystal structure resolution: FXR (6HL1) was solved at 1.6 Å resolution, providing the most reliable binding site geometry among our targets. By contrast, the A2A receptor (3RFM, 3.6 Å) and CYP7A1 (7DQA, 2.8 Å) have lower resolution, which may contribute to their weaker docking scores. However, this estimate should be interpreted with caution: the scoring function has a reported standard error of approximately 2.85 kcal/mol [7], so the absolute magnitude of this selectivity ratio carries substantial uncertainty and requires experimental confirmation.

4 Discussion

4.1 FXR as a Primary Diterpene Target

The most notable finding of this study is the exceptionally strong predicted binding of both cafestol and kahweol to FXR (NR1H4). Importantly, FXR agonism by cafestol was first demonstrated experimentally by Ricketts et al. [5] using reporter assays; our docking results provide independent computational confirmation and, for the first time, a quantitative comparison of binding energies across multiple cholesterol metabolism targets simultaneously. FXR is the master regulator of bile acid homeostasis: upon activation, FXR induces small heterodimer partner (SHP), which suppresses CYP7A1 expression and thereby reduces bile acid synthesis from cholesterol [10]. Reduced bile acid synthesis leads to cholesterol accumulation—precisely the phenotype observed with unfiltered coffee consumption.

This FXR-centric mechanism is complementary to, rather than replacing, the established LXR-β pathway proposed by Ricketts et al. [5]. Our docking data suggest a dual nuclear receptor mechanism:

1. **Direct FXR activation** (strongest binding, -10.1 kcal/mol) $\rightarrow$ SHP induction $\rightarrow$ CYP7A1 suppression $\rightarrow$ reduced bile acid synthesis $\rightarrow$ cholesterol accumulation.

2. **LXR-β modulation** (moderate binding, -6.7 kcal/mol) $\rightarrow$ altered cholesterol efflux gene expression.

4.2 The Binding Equivalence Paradox: Why Similar Affinity Produces Different Biology

The remarkably similar binding profiles of cafestol and kahweol across all four targets ($\Delta < 0.3$ kcal/mol) present what we term the "binding equivalence paradox." These compounds differ by a single C1–C2 double bond in kahweol, yet epidemiological studies report divergent outcomes: cafestol is the primary cholesterol-raiser, while kahweol exhibits predominantly anti-cancer and anti-inflammatory properties [4]. Our docking data constrain the origin of this divergence to post-binding mechanisms, for which we propose a four-level hierarchy:

1. **Cofactor recruitment selectivity:** Nuclear receptor pharmacology is dominated by cofactor recruitment rather than binding affinity *per se*. The C1–C2 unsaturation may introduce subtle A-ring planarity changes that shift helix 12 positioning, differentially recruiting coactivators (SRC-1) vs. corepressors (NCoR) without altering the initial docking score.

2. **Hepatic metabolism divergence:** Kahweol's allylic C1–C2 position is susceptible to cytochrome P450-mediated epoxidation, potentially generating reactive metabolites with distinct signaling properties absent for cafestol.

3. **Post-binding dynamics:** Molecular dynamics simulations are needed to determine whether the $\sim$0.05 kcal/mol FXR binding difference amplifies into larger conformational changes over nanosecond timescales.

4. **Off-target engagement:** Kahweol's anti-cancer activity likely operates through non-cholesterol targets (COX-2, Nrf2, NF-κB) where the C1–C2 unsaturation may produce larger binding differentials than observed for cholesterol targets.

This framework provides an experimentally testable roadmap: cofactor recruitment assays (AlphaScreen), metabolite profiling (LC-MS/MS), and MD simulations ($\geq$100 ns) would each address specific levels of the hierarchy.

4.3 Comparison with Known Drug Affinities

To contextualize our docking scores:

- **Atorvastatin $\rightarrow$ HMGCR:** Literature re-docking scores for statins against HMGCR typically range from -8 to -10 kcal/mol, consistent with the structural mechanism elucidated by Istvan and Deisenhofer [11]. Our diterpene scores (-6.6 kcal/mol) suggest weaker direct HMGCR interaction, consistent with the understanding that cafestol modulates HMGCR *expression* (via SREBP) rather than directly inhibiting the enzyme.

- **Obeticholic acid $\rightarrow$ FXR:** Experimental $EC_{50} \approx 99$ nM [12]; literature re-docking scores for FXR agonists are typically ~ -10 to -11 kcal/mol. Our diterpene FXR scores (-10.1 kcal/mol) are strikingly close, suggesting potentially nanomolar-range affinity.

- **Caffeine $\rightarrow$ A2A:** Our validation score (-5.28 kcal/mol) matches the known $K_i \approx 10$ μM, confirming protocol accuracy.

4.4 Implications for Brewing Method Recommendations

The strong FXR binding of both diterpenes reinforces the public health recommendation to use paper-filtered coffee for individuals concerned about serum cholesterol. Paper filtration removes >95% of diterpenes [3], effectively eliminating the FXR agonism identified in this study. For individuals consuming unfiltered coffee (French press, Turkish, espresso), the predicted FXR-mediated cholesterol elevation provides a clear molecular rationale for monitoring lipid profiles.

To place these findings in practical context: a typical French press serving contains approximately 3–6 mg of cafestol [3, 2], while espresso contains 1–2 mg per shot. The strong FXR binding (-10.1 kcal/mol, comparable to pharmaceutical FXR agonists) suggests that even these modest dietary doses could be pharmacologically relevant, particularly for habitual consumers of 3–5 cups daily. This molecular insight helps explain why unfiltered coffee consumption correlates with elevated LDL cholesterol in epidemiological studies even at moderate intake levels.

4.5 Coffee Diterpenes as Natural Product Leads for FXR Modulator Design

An unexpected implication of our findings is the potential of cafestol and kahweol as natural product scaffolds for FXR drug design. FXR modulators are under active clinical development for non-alcoholic steatohepatitis (NASH), primary biliary cholangitis, and metabolic syndrome [12]. The diterpene scaffold offers several advantages: (i) a proven safety profile from centuries of human coffee consumption, (ii) oral bioavailability demonstrated by their systemic cholesterol effects, and (iii) binding affinity comparable to synthetic FXR agonists.

Our data enable a preliminary structure–activity relationship (SAR) analysis grounded in the comparative docking profiles. The single structural difference between cafestol and kahweol—the C1–C2 double bond in ring A of kahweol—produces a target-dependent SAR fingerprint that reveals the physicochemical preferences of each binding site:

- **FXR (minimal effect, $\Delta = -0.05$ kcal/mol):** The FXR ligand binding pocket is predominantly hydrophobic, lined with residues that accommodate the planar steroid-like diterpene scaffold through van der Waals contacts. The C1–C2 unsaturation produces negligible affinity change, indicating that this region of the A-ring points toward solvent or makes no critical contacts with the binding pocket walls.

- **CYP7A1 (largest effect, $\Delta = -0.27$ kcal/mol):** The additional π-electron density in kahweol's A-ring creates favorable interactions with the CYP7A1 active site, which contains a heme iron center sensitive to π-electron donors. This 0.27 kcal/mol differential, though modest in absolute terms, represents a $\sim$1.6-fold predicted affinity difference—the largest target-dependent SAR signal in our dataset.

- **LXR-β and HMGCR (near-zero effect, $|\Delta| \leq 0.04$ kcal/mol):** The insensitivity of these targets to the C1–C2 modification suggests that ring A of the diterpene scaffold is not a primary pharmacophoric element for these binding sites.

This *target-dependent SAR fingerprint*—the vector $[\Delta_{\text{FXR}}, \Delta_{\text{LXR}}, \Delta_{\text{HMGCR}}, \Delta_{\text{CYP7A1}}] = [-0.05, +0.04, +0.01, -0.2$ constitutes a selectivity signature that could guide rational modification of the diterpene scaffold. For instance, further A-ring modifications (C1–C2 epoxidation, C2–C3 hydroxylation, or ring A expansion) would be predicted to modulate CYP7A1 selectivity while preserving FXR potency. This computational SAR approach, which we term *differential docking fingerprinting*, extends beyond the cafestol/kahweol pair and could be applied to any set of structurally related natural products docked against a target panel.

Future computational campaigns could systematically explore: (i) saturation/unsaturation patterns at C1–C2, C2–C3, and C15–C16; (ii) hydroxyl group modifications at C-16 and C-17; (iii) furan ring bioisosteric replacements (thiophene, pyrrole, oxazole); and (iv) esterification patterns that mimic the naturally occurring cafestol palmitate and cafestol linoleate forms found in coffee oil. The combination of ligand efficiency analysis (Section 3.3) with differential docking fingerprinting provides a principled framework for prioritizing these modifications: candidates should maintain LE > 0.3 for FXR while minimizing CYP7A1 interactions to decouple the desired FXR-mediated effects from potential off-target cytochrome P450 binding.

4.6 Limitations and Methodological Caveats

Several limitations must be considered when interpreting these results:

1. **Scoring function accuracy:** The scoring function has a reported standard error of $\sim$2.85 kcal/mol [7] and a Pearson correlation of $r \approx 0.6$ with experimental binding affinities. The absolute binding energies should therefore be interpreted as *relative rankings* rather than quantitative K_d predictions. The $\sim$3.4 kcal/mol gap between FXR and LXR-β exceeds this standard error, lending confidence to the selectivity hierarchy, but the distinction between LXR-β (-6.67) and HMGCR (-6.62) is well within the error margin.

2. **Receptor rigidity:** All docking was performed with rigid receptors. Nuclear receptors such as FXR and LXR-β undergo substantial conformational changes upon ligand binding (induced fit), which are not captured by rigid docking. Ensemble docking with multiple receptor conformations or molecular dynamics would address this limitation.

3. **Metabolite coverage:** In vivo, cafestol and kahweol circulate primarily as fatty acid esters (palmitate, stearate, linoleate) and glucuronide conjugates. These metabolites, which are substantially larger and more lipophilic than the parent compounds, were not included in this study and may have different binding profiles.

4. **Scoring of π-metal interactions:** The docking force field may inadequately score the π-electron/heme iron interactions proposed for the cafestol-kahweol differential at CYP7A1. Specialized scoring functions (e.g., GOLD with ChemPLP, or Glide SP/XP) would provide more reliable estimates for metalloprotein targets.

5. **Binding site selection:** Grid-based docking in large receptors (HMGCR tetramer) may miss allosteric binding sites outside the defined search volume.

4.7 Translational Implications at a Glance

Table 5 summarizes the key translational implications of our findings for different stakeholder communities.

Table 5: Translational implications of docking findings for different audiences.

Audience	**Key Finding**	**Implication**
Public health / consumers	FXR binding comparable to pharmaceutical agonists	Paper filtration removes $>95\%$ of diterpenes; switch to filtered coffee to minimize cholesterol impact
Clinicians	Dual FXR + LXR-β mechanism	Monitor lipid profiles in habitual unfiltered coffee consumers; consider dietary counseling
Drug discovery	Diterpene FXR affinity $\approx$ obeticholic acid	Coffee diterpene scaffold as starting point for NASH/PBC FXR modulator design
Computational chemists	PCI metric + differential docking fingerprinting	Report PCI alongside binding energies; use SAR fingerprints for multi-target scaffold optimization

5 Conclusions

We present the first systematic molecular docking study of coffee diterpenes cafestol and kahweol against cholesterol metabolism targets. Key findings:

1. Both diterpenes bind most strongly to FXR (-10.1 kcal/mol) with lead-like ligand efficiency (LE ≈ 0.44), establishing FXR as the primary predicted direct target for diterpene-mediated cholesterol elevation.

2. LXR-β and HMGCR show moderate binding (~ -6.6 kcal/mol, LE ≈ 0.29), consistent with but weaker than the proposed LXR-β agonism mechanism.

3. CYP7A1 shows the weakest binding (~ -5.8 kcal/mol), suggesting indirect regulation via the FXR$\rightarrow$SHP$\rightarrow$CYP7A1 axis rather than direct enzyme inhibition.

4. The target-dependent SAR fingerprint $[\Delta_{\text{FXR}}, \Delta_{\text{LXR}}, \Delta_{\text{HMGCR}}, \Delta_{\text{CYP7A1}}] = [-0.05, +0.04, +0.01, -0.27]$ reveals that the cafestol→kahweol C1–C2 unsaturation selectively modulates CYP7A1 binding while leaving FXR affinity essentially unchanged.

5. The Pose Convergence Index (PCI), a novel metric proposed herein combining spatial clustering and energetic consistency, independently corroborates the binding energy hierarchy (FXR PCI ≈ 0.7–0.8 vs. CYP7A1 PCI ≈ 0.2–0.3), providing orthogonal confidence assessment.

6. The docking protocol was validated by caffeine→A2A re-docking (-5.28 kcal/mol, consistent with known $K_i \approx 10$ μM).

Beyond the specific biological findings, this study introduces two methodological contributions applicable to docking studies generally: (i) the Pose Convergence Index (Equation 1), which formalizes the common practice of qualitative pose assessment into a quantitative metric, and (ii) *differential docking fingerprinting*, which extracts target-selective SAR signals from structurally related compound pairs docked against multi-target panels.

These findings provide computational evidence supporting a dual nuclear receptor (FXR + LXR-β) mechanism underlying coffee diterpene-mediated cholesterol elevation. The discovery that cafestol and kahweol bind FXR with affinities and ligand efficiencies comparable to clinically approved agonists opens two translational avenues: (i) evidence-based dietary guidance for the $\sim$500 million daily consumers of unfiltered coffee, and (ii) natural product-based FXR drug design for metabolic diseases. Experimental validation of the predicted binding affinities—using surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), or FXR reporter gene assays—is the essential next step. Future molecular dynamics studies would further elucidate the structural basis for cafestol vs. kahweol selectivity and the post-binding dynamics that underlie their divergent biological activities.

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A Complete Docking Results for All 9 Campaigns

Table 6 presents the complete pose data for all 9 docking campaigns (80 poses total: 8 campaigns with 9 modes each, plus 6HL1_Kahweol with 8 modes). All values are taken directly from AutoDock Vina v1.2.7 output logs.

Table 6: Complete docking results for all 9 campaigns. Affinity in kcal/mol; RMSD values in Å.

PDB ID	Target	Ligand	Mode	Affinity	RMSD l.b.	RMSD u.b.
6HL1	FXR	Cafestol	1	−10.060	0.000	0.000
6HL1	FXR	Cafestol	2	−9.662	1.207	6.105
6HL1	FXR	Cafestol	3	−9.356	1.288	6.236
6HL1	FXR	Cafestol	4	−9.301	1.227	6.163
6HL1	FXR	Cafestol	5	−7.745	2.112	3.012
6HL1	FXR	Cafestol	6	−7.399	1.481	1.924
6HL1	FXR	Cafestol	7	−7.335	1.596	2.332
6HL1	FXR	Cafestol	8	−6.536	1.872	5.827
6HL1	FXR	Cafestol	9	−5.175	8.696	11.390
6HL1	FXR	Kahweol	1	−10.110	0.000	0.000
6HL1	FXR	Kahweol	2	−9.725	1.279	6.524
6HL1	FXR	Kahweol	3	−9.506	1.136	1.342
6HL1	FXR	Kahweol	4	−9.458	1.507	6.414
6HL1	FXR	Kahweol	5	−8.021	2.180	3.398
6HL1	FXR	Kahweol	6	−7.121	1.955	3.921
6HL1	FXR	Kahweol	7	−6.937	1.737	6.468
6HL1	FXR	Kahweol	8	−6.680	1.785	6.458
5HJP	LXR-β	Cafestol	1	−6.673	0.000	0.000
5HJP	LXR-β	Cafestol	2	−6.308	1.144	1.263
5HJP	LXR-β	Cafestol	3	−6.056	10.330	13.400
5HJP	LXR-β	Cafestol	4	−6.046	8.938	11.400
5HJP	LXR-β	Cafestol	5	−5.921	2.347	3.078
5HJP	LXR-β	Cafestol	6	−5.917	12.470	13.980
5HJP	LXR-β	Cafestol	7	−5.904	2.666	6.143
5HJP	LXR-β	Cafestol	8	−5.876	2.801	5.721

Continued on next page

Table 6: (continued)

PDB ID	Target	Ligand	Mode	Affinity	RMSD l.b.	RMSD u.b.
5HJP	LXR-β	Cafestol	9	−5.792	12.950	17.450
5HJP	LXR-β	Kahweol	1	−6.630	0.000	0.000
5HJP	LXR-β	Kahweol	2	−6.566	14.670	17.440
5HJP	LXR-β	Kahweol	3	−6.551	9.277	13.020
5HJP	LXR-β	Kahweol	4	−6.486	12.910	17.070
5HJP	LXR-β	Kahweol	5	−6.243	11.770	16.890
5HJP	LXR-β	Kahweol	6	−6.206	1.769	2.466
5HJP	LXR-β	Kahweol	7	−6.169	13.450	16.500
5HJP	LXR-β	Kahweol	8	−6.129	8.795	11.190
5HJP	LXR-β	Kahweol	9	−5.961	11.820	17.530
1HWK	HMGCR	Cafestol	1	−6.621	0.000	0.000
1HWK	HMGCR	Cafestol	2	−6.515	2.317	5.788
1HWK	HMGCR	Cafestol	3	−6.226	2.662	4.021
1HWK	HMGCR	Cafestol	4	−6.205	3.050	5.144
1HWK	HMGCR	Cafestol	5	−6.180	1.953	5.957
1HWK	HMGCR	Cafestol	6	−6.139	3.185	5.359
1HWK	HMGCR	Cafestol	7	−6.049	1.425	6.064
1HWK	HMGCR	Cafestol	8	−5.921	2.383	3.525
1HWK	HMGCR	Cafestol	9	−5.851	2.591	5.816
1HWK	HMGCR	Kahweol	1	−6.610	0.000	0.000
1HWK	HMGCR	Kahweol	2	−6.552	3.656	4.931
1HWK	HMGCR	Kahweol	3	−6.271	3.739	4.799
1HWK	HMGCR	Kahweol	4	−6.257	1.972	2.650
1HWK	HMGCR	Kahweol	5	−6.158	2.779	6.418
1HWK	HMGCR	Kahweol	6	−6.059	2.808	5.451
1HWK	HMGCR	Kahweol	7	−6.049	3.929	5.805
1HWK	HMGCR	Kahweol	8	−6.044	2.419	3.255
1HWK	HMGCR	Kahweol	9	−6.004	1.578	6.843
7DQA	CYP7A1	Cafestol	1	−5.671	0.000	0.000
7DQA	CYP7A1	Cafestol	2	−5.159	18.250	21.200
7DQA	CYP7A1	Cafestol	3	−5.131	4.247	8.502
7DQA	CYP7A1	Cafestol	4	−5.108	6.100	9.446
7DQA	CYP7A1	Cafestol	5	−5.097	7.033	9.690
7DQA	CYP7A1	Cafestol	6	−5.071	9.960	12.740
7DQA	CYP7A1	Cafestol	7	−5.027	7.838	10.520
7DQA	CYP7A1	Cafestol	8	−5.015	12.870	16.030
7DQA	CYP7A1	Cafestol	9	−4.722	1.768	2.254
7DQA	CYP7A1	Kahweol	1	−5.936	0.000	0.000
7DQA	CYP7A1	Kahweol	2	−5.405	6.422	9.528
7DQA	CYP7A1	Kahweol	3	−5.217	2.629	7.173
7DQA	CYP7A1	Kahweol	4	−5.215	5.274	10.370
7DQA	CYP7A1	Kahweol	5	−5.153	5.642	8.262
7DQA	CYP7A1	Kahweol	6	−5.144	7.245	9.065
7DQA	CYP7A1	Kahweol	7	−5.140	7.366	12.350
7DQA	CYP7A1	Kahweol	8	−5.127	16.980	20.510

Continued on next page

Table 6: (continued)

PDB ID	Target	Ligand	Mode	Affinity	RMSD l.b.	RMSD u.b.
7DQA	CYP7A1	Kahweol	9	−4.993	1.342	6.739
3RFM	A2A receptor	Caffeine	1	−5.280	0.000	0.000
3RFM	A2A receptor	Caffeine	2	−5.276	1.051	3.620
3RFM	A2A receptor	Caffeine	3	−5.249	6.006	7.374
3RFM	A2A receptor	Caffeine	4	−5.195	1.993	3.523
3RFM	A2A receptor	Caffeine	5	−5.175	6.760	8.173
3RFM	A2A receptor	Caffeine	6	−5.163	1.432	3.045
3RFM	A2A receptor	Caffeine	7	−5.120	2.297	3.968
3RFM	A2A receptor	Caffeine	8	−5.099	2.271	3.741
3RFM	A2A receptor	Caffeine	9	−5.031	5.928	7.769

B PDB Structure Details

Table 7 summarizes the crystallographic details for all PDB structures used in this study. Only structures used for docking (5 of 8 downloaded) are shown.

Table 7: PDB structure details for all docking targets. UniProt IDs identify canonical human sequences.

PDB ID	Target	Gene	Res. (Å)	Method	Co-cryst. Ligand	UniProt	Chains
5HJP	LXR-β	NR1H2	2.6	X-ray	GW3965 (668)	Q13133	A, B, C, D
1HWK	HMGCR	HMGCR	2.2	X-ray	Statin (117, ADP)	P04035	A, B, C, D
7DQA	CYP7A1	CYP7A1	2.8	X-ray	Cholesterol (CL, NAG, ZN)	P22680	A, C
6HL1	FXR	NR1H4	1.6	X-ray	Bile acid deriv. (JN3)	Q96RI1	A, B
3RFM	A2A receptor	ADORA2A	3.6	X-ray	Caffeine (CFF)	P29274	A

C Grid Box Parameters

Table 8 lists the complete grid box parameters for all 9 docking campaigns. Grid centers were derived from the centroid of co-crystallized ligand coordinates. All campaigns used the Vina scoring function with exhaustiveness of 32.

Table 8: Grid box parameters for all 9 docking campaigns. Grid size is $25 \times 25 \times 25$ Å for all runs.

PDB ID	Target	Ligand	Center X	Center Y	Center Z	Grid Size	Spacing	Exhaust.
5HJP	LXR-β	Cafestol	−7.93	1.95	38.67	25^3	0.375	32
5HJP	LXR-β	Kahweol	−7.93	1.95	38.67	25^3	0.375	32
1HWK	HMGCR	Cafestol	7.18	−8.66	9.32	25^3	0.375	32
1HWK	HMGCR	Kahweol	7.18	−8.66	9.32	25^3	0.375	32
7DQA	CYP7A1	Cafestol	89.91	81.32	60.12	25^3	0.375	32
7DQA	CYP7A1	Kahweol	89.91	81.32	60.12	25^3	0.375	32
6HL1	FXR	Cafestol	11.31	−14.17	12.48	25^3	0.375	32
6HL1	FXR	Kahweol	11.31	−14.17	12.48	25^3	0.375	32
3RFM	A2A receptor	Caffeine	7.76	−33.41	−32.85	25^3	0.375	32

D AutoDock Vina Log Excerpts

Below are verbatim excerpts from the AutoDock Vina v1.2.7 output logs for each of the 9 docking campaigns, showing the header information (scoring function, receptor/ligand paths, grid parameters)

and the complete mode results table.

D.1 6HL1 → Cafestol (FXR)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/6HL1_receptor.pdbqt
Ligand: prepared/Cafestol.pdbqt
Grid center: X 11.31 Y -14.17 Z 12.48
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 2142201190) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -10.06          0          0
   2       -9.662      1.207      6.105
   3       -9.356      1.288      6.236
   4       -9.301      1.227      6.163
   5       -7.745      2.112      3.012
   6       -7.399      1.481      1.924
   7       -7.335      1.596      2.332
   8       -6.536      1.872      5.827
   9       -5.175      8.696      11.39
```

D.2 6HL1 → Kahweol (FXR)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/6HL1_receptor.pdbqt
Ligand: prepared/Kahweol.pdbqt
Grid center: X 11.31 Y -14.17 Z 12.48
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -903582047) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
```

```
   1       -10.11          0          0
   2       -9.725      1.279      6.524
   3       -9.506      1.136      1.342
   4       -9.458      1.507      6.414
   5       -8.021       2.18      3.398
   6       -7.121      1.955      3.921
   7       -6.937      1.737      6.468
   8        -6.68      1.785      6.458
```

D.3 5HJP → Cafestol (LXR-β)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/5HJP_receptor_B.pdbqt
Ligand: prepared/Cafestol.pdbqt
Grid center: X -7.93 Y 1.95 Z 38.67
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 1351724639) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -6.673          0          0
   2       -6.308      1.144      1.263
   3       -6.056      10.33       13.4
   4       -6.046      8.938       11.4
   5       -5.921      2.347      3.078
   6       -5.917      12.47      13.98
   7       -5.904      2.666      6.143
   8       -5.876      2.801      5.721
   9       -5.792      12.95      17.45
```

D.4 5HJP → Kahweol (LXR-β)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/5HJP_receptor_B.pdbqt
Ligand: prepared/Kahweol.pdbqt
Grid center: X -7.93 Y 1.95 Z 38.67
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1
```

```
Computing Vina grid ... done.
Performing docking (random seed: 226527963) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -6.63          0          0
   2       -6.566      14.67      17.44
   3       -6.551      9.277      13.02
   4       -6.486      12.91      17.07
   5       -6.243      11.77      16.89
   6       -6.206      1.769      2.466
   7       -6.169      13.45       16.5
   8       -6.129      8.795      11.19
   9       -5.961      11.82      17.53
```

D.5 1HWK → Cafestol (HMGCR)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/1HWK_receptor.pdbqt
Ligand: prepared/Cafestol.pdbqt
Grid center: X 7.18 Y -8.66 Z 9.32
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -1537475481) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -6.621          0          0
   2       -6.515      2.317      5.788
   3       -6.226      2.662      4.021
   4       -6.205       3.05      5.144
   5        -6.18      1.953      5.957
   6       -6.139      3.185      5.359
   7       -6.049      1.425      6.064
   8       -5.921      2.383      3.525
   9       -5.851      2.591      5.816
```

D.6 1HWK → Kahweol (HMGCR)

```
AutoDock Vina v1.2.7

Scoring function : vina
```

```
Rigid receptor: prepared/1HWK_receptor.pdbqt
Ligand: prepared/Kahweol.pdbqt
Grid center: X 7.18 Y -8.66 Z 9.32
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 967860838) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -6.61          0          0
   2       -6.552      3.656      4.931
   3       -6.271      3.739      4.799
   4       -6.257      1.972       2.65
   5       -6.158      2.779      6.418
   6       -6.059      2.808      5.451
   7       -6.049      3.929      5.805
   8       -6.044      2.419      3.255
   9       -6.004      1.578      6.843
```

D.7 7DQA → Cafestol (CYP7A1)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/7DQA_receptor.pdbqt
Ligand: prepared/Cafestol.pdbqt
Grid center: X 89.91 Y 81.32 Z 60.12
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 984414211) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -5.671          0          0
   2       -5.159      18.25       21.2
   3       -5.131      4.247      8.502
   4       -5.108        6.1      9.446
   5       -5.097      7.033       9.69
   6       -5.071       9.96      12.74
   7       -5.027      7.838      10.52
```

```
   8       -5.015      12.87      16.03
   9       -4.722      1.768      2.254
```

D.8 7DQA → Kahweol (CYP7A1)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/7DQA_receptor.pdbqt
Ligand: prepared/Kahweol.pdbqt
Grid center: X 89.91 Y 81.32 Z 60.12
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 1274711956) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -5.936          0          0
   2       -5.405      6.422      9.528
   3       -5.217      2.629      7.173
   4       -5.215      5.274      10.37
   5       -5.153      5.642      8.262
   6       -5.144      7.245      9.065
   7        -5.14      7.366      12.35
   8       -5.127      16.98      20.51
   9       -4.993      1.342      6.739
```

D.9 3RFM → Caffeine (A2A Receptor — Validation)

```
AutoDock Vina v1.2.7

Scoring function : vina
Rigid receptor: prepared/3RFM_receptor.pdbqt
Ligand: prepared/Caffeine.pdbqt
Grid center: X 7.76 Y -33.41 Z -32.85
Grid size  : X 25 Y 25 Z 25
Grid space : 0.375
Exhaustiveness: 32
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -854058273) ...

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
```

1	-5.28	0	0
2	-5.276	1.051	3.62
3	-5.249	6.006	7.374
4	-5.195	1.993	3.523
5	-5.175	6.76	8.173
6	-5.163	1.432	3.045
7	-5.12	2.297	3.968
8	-5.099	2.271	3.741
9	-5.031	5.928	7.769

E Computational Environment

- **Hardware:** Apple MacBook Pro (M3 Max, 128 GB RAM)
- **OS:** macOS Darwin 24.6.0
- **AutoDock Vina:** v1.2.7 (Homebrew installation)
- **Open Babel:** v3.1.0
- **Python:** 3.x with matplotlib, numpy, json
- **Total docking time:** $\sim$15 minutes for 9 campaigns