Why Filtered Coffee Doesn't Raise Cholesterol: A Molecular Docking Explanation

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Elena Zueco[1,*] and Enrique Zueco[2]

[1]University of Geneva, Switzerland [2]Zytech Computational Sciences, Spain
[*]elena.zueco@unige.ch

Background: Coffee is consumed by 2.25 billion people daily, yet the molecular mechanism by which unfiltered coffee raises serum cholesterol remains computationally unexplored. The diterpenes cafestol and kahweol, present in French press and Turkish coffee but removed by paper filtration, increase LDL cholesterol by 6–8% in meta-analyses. However, no molecular docking study has investigated how these compounds interact with cholesterol metabolism targets at the atomic level.

Methods: We performed molecular docking of cafestol, kahweol, and caffeine (control) against four key cholesterol and bile acid metabolism targets: liver X receptor alpha (LXR-α, PDB: 5HJP, $2.6\,$Å), HMG-CoA reductase (HMGCR, PDB: 1HWK, $2.2\,$Å), cholesterol 7α-hydroxylase (CYP7A1, PDB: 7DQA, $2.8\,$Å), and farnesoid X receptor (FXR, PDB: 6HL1, $1.6\,$Å). Docking was performed using AutoDock Vina v1.2.7 with exhaustiveness = 32 and a $25\,$Å cubic grid box centered on each co-crystallized ligand. Validation was performed by re-docking co-crystallized ligands.

Results: The strongest predicted binding was to FXR, not LXR-α as conventionally assumed: cafestol bound FXR with $\Delta G = -10.06$ kcal/mol and kahweol with $\Delta G = -10.11$ kcal/mol, corresponding to estimated K_d values in the low nanomolar range. LXR-α binding was substantially weaker (cafestol: -6.67 kcal/mol; kahweol: -6.63 kcal/mol), as was HMGCR binding (cafestol: -6.62; kahweol: -6.61 kcal/mol). CYP7A1 showed the weakest affinity (cafestol: -5.67; kahweol: -5.94 kcal/mol). Caffeine, as a negative control, showed weak A_{2A} receptor binding (-5.28 kcal/mol) and negligible interaction with cholesterol targets. Both diterpenes showed nearly identical binding at every target (differences < 0.3 kcal/mol), consistent with their similar cholesterol-raising effects but contrasting with their divergent anti-cancer profiles reported in the literature.

Significance: This is the **first molecular docking study of coffee diterpenes against cholesterol metabolism targets**. Our findings identify FXR as the strongest predicted binding partner for both cafestol and kahweol, suggesting a FXR→SHP→CYP7A1 mechanism for coffee-induced hypercholesterolemia that complements the established LXR-α pathway. The near-identical docking profiles of cafestol and kahweol indicate that their differential biological effects arise from post-binding events (cofactor recruitment, metabolism) rather than initial target recognition. These results provide a computational rationale for the well-established clinical observation that paper filtration protects cardiovascular health by removing diterpenes that activate nuclear receptors controlling cholesterol homeostasis.

Keywords: coffee, cafestol, kahweol, molecular docking, cholesterol, FXR, LXR-alpha, HMGCR,

CYP7A1, brewing method, cardiovascular health