RESEARCH PAPER

# COMPARATIVE IN SILICO EVALUATION OF QUERCETIN, KAEMPFEROL, CHLOROGENIC ACID AND CAFFEIC ACID AGAINST JAK3 KINASE AND 5A-REDUCTASE TYPE II: MOLECULAR DOCKING AND ADMET ASSESSMENT FOR HAIR-GROWTH RESEARCH

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**ABSTRACT:**
**Background:** Hair follicle biology is influenced by inflammatory signaling and androgen metabolism. JAK3-related signaling and 5α-reductase type II (SRD5A2) therefore represent mechanistically distinct targets relevant to hair-loss research. **Objective:** To comparatively characterize the predicted binding of four phytoconstituents quercetin, kaempferol, chlorogenic acid and caffeic acid to JAK3 and SRD5A2, using tofacitinib and finasteride as reference compounds, and to assess the supplied pkCSM ADMET profiles. **Methods:** AutoDock Vina docking outputs were analyzed for JAK3 (PDB 3LXK) and SRD5A2 (PDB 7BW1), followed by 2D/3D interaction analysis. ADMET values were taken from the supplied pkCSM dataset. **Results:** For JAK3, quercetin showed the most favorable predicted affinity (−9.147 kcal/mol), followed by kaempferol (−8.833), tofacitinib (−8.140), chlorogenic acid (−7.937) and caffeic acid (−6.555). For SRD5A2, finasteride showed the most favorable score (−7.797), followed by quercetin (−6.414), kaempferol (−6.308), caffeic acid (−5.869) and chlorogenic acid (−5.616). Quercetin and kaempferol were predicted to have skin permeability values of −2.735 and −3.493 log Kp, respectively. Kaempferol was predicted positive for AMES mutagenicity, whereas quercetin, chlorogenic acid and caffeic acid were predicted negative. **Conclusion:** The combined dataset identifies quercetin and kaempferol as the strongest JAK3-scoring phytoconstituents, while finasteride remains the strongest SRD5A2 reference ligand. These results are hypothesis-generating and require experimental target-inhibition, dermal-delivery, safety and hair-growth validation.
***Keywords:*** Quercetin; Kaempferol; Chlorogenic acid; Caffeic acid; JAK3; 5α-reductase type II; SRD5A2; AutoDock Vina; ADMET; hair growth; phytoconstituents.
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## INTRODUCTION:

Hair growth is a cyclic biological process involving anagen, catagen and telogen phases. Dysregulation of inflammatory signaling, follicular signaling pathways and androgen metabolism can contribute to hair loss. Recent reviews emphasize that phytochemicals may influence follicular signaling and hair-growth biology, but translation to therapeutic use requires mechanistic and delivery validation. [1–3]

JAK/STAT signaling has attracted attention in inflammatory hair disorders, whereas 5α-reductase-mediated conversion of testosterone to dihydrotestosterone is central to androgen-dependent follicular miniaturization. Tofacitinib and finasteride were therefore selected as pharmacological reference compounds for JAK3 and SRD5A2, respectively. [4–8] The present study expands the supplied dataset by comparing four phytoconstituents across both targets rather than restricting the analysis to two flavonoids.

A recent 2025 computational study also evaluated phytochemicals against 5α-reductase in the context of hair-growth research and used molecular docking together with additional computational analyses, supporting the relevance of structure-based screening to this research question. [9]

The objective of this work was to integrate the supplied molecular docking, interaction-map and ADMET datasets into a publication-oriented comparative analysis, while explicitly distinguishing computational

predictions from experimentally demonstrated biological activity.

**MATERIALS AND METHODS:**

**Ligand and reference-drug selection**

Quercetin, kaempferol, chlorogenic acid and caffeic acid were evaluated as phytoconstituents. Tofacitinib was used as the JAK3 reference drug and finasteride as the SRD5A2 reference inhibitor.

**Protein targets**

JAK3 kinase was represented by PDB ID 3LXK and SRD5A2 (5α-reductase type II) by PDB ID 7BW1, based on the supplied docking-results report. These identifiers should be checked against the original downloaded PDB files before submission.

**Molecular docking**

Molecular docking was performed with AutoDock Vina. For the supplied JAK3 workflow, the grid center was X = −4.95575, Y = 13.0804, Z = 17.0951; grid size was 22.5 × 22.5 × 22.5 Å; grid spacing was 0.375 Å; and exhaustiveness was 8. The supplied JAK3 outputs used the same displayed grid settings. The best-ranked pose was used for subsequent interaction interpretation. AutoDock Vina is an established open-source docking platform. [10,11]

**Binding-interaction analysis**

The supplied 2D and 3D interaction maps were interpreted using the interaction labels shown in the source figures, including van der Waals, π-alkyl, π-sigma, alkyl, carbon–hydrogen and aromatic interactions. The interaction maps were treated as structural support for the predicted poses rather than direct evidence of enzyme inhibition.

**ADMET prediction**

Absorption, distribution, metabolism, excretion and toxicity parameters were taken from the supplied pkCSM outputs. The dataset included water solubility, Caco-2 permeability, human intestinal absorption, skin permeability (log Kp), P-glycoprotein status, distribution parameters, CYP-related predictions, clearance and toxicity endpoints. pkCSM values are computational predictions rather than experimental measurements. [12]

**RESULTS:**

**Comparative docking performance**

The combined docking dataset is summarized in Table 1. A more negative AutoDock Vina score represents a more favorable predicted affinity within the same docking protocol; scores should not be interpreted as experimentally measured binding constants.

***Table 1. Comparative best-ranked docking affinities from the supplied AutoDock Vina outputs.***

| Target | Compound | Role | Best affinity (kcal/mol) | Rank |
|---|---|---|---|---|
| JAK3 (3LXK) | Quercetin | Phytoconstituent | −9.147 | 1 |
| JAK3 (3LXK) | Kaempferol | Phytoconstituent | −8.833 | 2 |
| JAK3 (3LXK) | Tofacitinib | Reference drug | −8.140 | 3 |
| JAK3 (3LXK) | Chlorogenic acid | Phytoconstituent | −7.937 | 4 |
| JAK3 (3LXK) | Caffeic acid | Phytoconstituent | −6.555 | 5 |
| SRD5A2 (7BW1) | Finasteride | Reference inhibitor | −7.797 | 1 |
| SRD5A2 (7BW1) | Quercetin | Phytoconstituent | −6.414 | 2 |
| SRD5A2 (7BW1) | Kaempferol | Phytoconstituent | −6.308 | 3 |
| SRD5A2 (7BW1) | Caffeic acid | Phytoconstituent | −5.869 | 4 |
| SRD5A2 (7BW1) | Chlorogenic acid | Phytoconstituent | −5.616 | 5 |

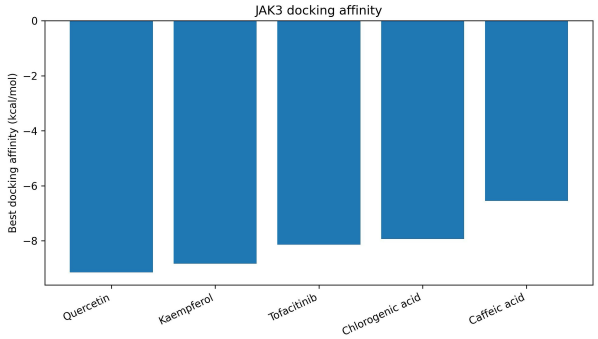


***Figure 1. Comparative JAK3 docking scores for quercetin, kaempferol, tofacitinib, chlorogenic acid and caffeic acid. More negative values indicate more favorable predicted affinity within the same protocol.***

Quercetin produced the most favorable JAK3 score (−9.147 kcal/mol), 1.007 kcal/mol more negative than tofacitinib. Kaempferol was also more negative than tofacitinib by 0.693 kcal/mol. Chlorogenic acid was slightly less negative than tofacitinib (difference 0.203 kcal/mol), whereas caffeic acid showed the weakest JAK3 score among the five compounds.

**JAK3 interaction analysis**


***Figure 2. Supplied AutoDock Vina docking outputs for tofacitinib, quercetin and kaempferol against JAK3 (3LXK).***

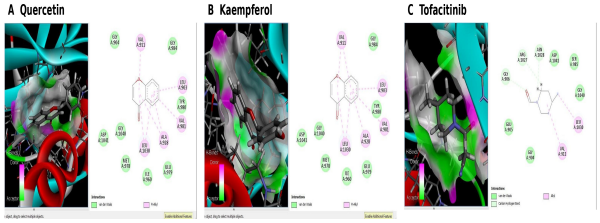


***Figure 3. Supplied 3D/2D interaction maps for quercetin, kaempferol and tofacitinib at JAK3. The maps show the interaction environments described in the supplied dataset.***

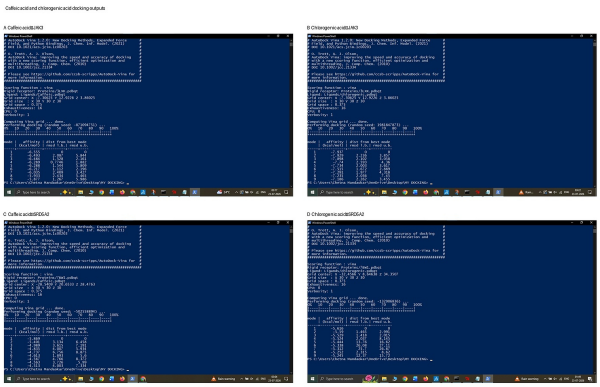

***Figure 4. Caffeic acid and chlorogenic acid docking outputs against JAK3 and SRD5A2 from the supplied docking-results report.***

The JAK3 interaction maps showed van der Waals and π-alkyl interactions for quercetin and kaempferol, whereas tofacitinib showed carbon–hydrogen, van der Waals and alkyl interactions. The detailed caffeic-acid/JAK3 map showed van der Waals contacts involving CYS A:909, PRO A:906, TYR A:904, LEU A:905, VAL A:884, GLY A:829 and carbon–hydrogen bonding involving GLY A:908, with π-sigma/π-alkyl contacts involving ALA A:853, LEU A:828, VAL A:836 and LEU A:956. Chlorogenic acid/JAK3 showed van der Waals contacts involving ALA A:966, LYS A:855, ASP A:967, SER A:835, LYS A:830, GLY A:829, ARG A:953 and ASN A:954, with an alkyl contact involving VAL A:836. These residue-level observations support the poses but do not establish inhibition.

**SRD5A2 docking and interaction analysis**


***Figure 5. Supplied AutoDock Vina docking outputs for finasteride, quercetin and kaempferol against SRD5A2 (7BW1).***

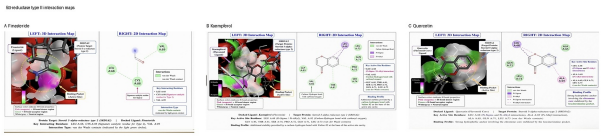

***Figure 6. Supplied 3D/2D interaction maps for finasteride, kaempferol and quercetin at SRD5A2.***

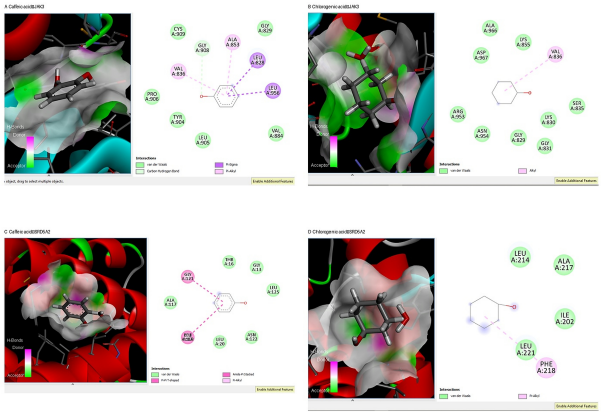

***Figure 7. Caffeic acid and chlorogenic acid interaction maps at JAK3 and SRD5A2 from the supplied docking-results report.***

Finasteride showed the most favorable SRD5A2 affinity (−7.797 kcal/mol). Quercetin (−6.414 kcal/mol) and kaempferol (−6.308 kcal/mol) were weaker than finasteride but showed moderately negative predicted affinities. Caffeic acid (−5.869 kcal/mol) and chlorogenic acid (−5.616 kcal/mol) were weaker than the reference and flavonoids in the supplied protocol.

Finasteride showed van der Waals contacts with LEU A:68, CYS A:88 and VAL A:89. Kaempferol showed π-sigma/π-alkyl interactions involving LEU A:68, a carbon–hydrogen interaction with the carbonyl oxygen, and van der Waals contacts involving GLY A:85, THR A:81, SER A:74, PRO A:72, GLN A:71 and LEU A:73; the supplied map also indicated a carbon–hydrogen interaction involving VAL A:82. Quercetin showed π-sigma/π-alkyl interactions involving LEU A:68 and ALA A:69 and van der Waals contacts involving ALA A:65, GLN A:71 and LEU A:73.

For caffeic acid/SRD5A2, the supplied interaction map showed van der Waals contacts involving THR A:16, GLY A:13, LEU A:125, ALA A:117, LEU A:20 and ASN A:122, with π–π T-shaped interaction at GLY A:121 and amide–π stacking at PHE A:118. Chlorogenic acid/SRD5A2 showed van der Waals contacts with LEU A:214, ALA A:217, ILE A:202 and LEU A:221, together with a π-alkyl interaction involving PHE A:218.

**ADMET profiling**

***Table 2. Selected ADMET predictions from the supplied pkCSM datasets. Values are model predictions, not experimental measurements.***

| Parameter | Quercetin | Kaempferol | Chlorogenic acid | Caffeic acid |
|---|---|---|---|---|
| Water solubility (log mol/L) | −2.925 | −3.251 | −2.449 | −2.330 |
| Caco-2 permeability | −0.229 | +0.270 | −0.840 | +0.634 |
| Human intestinal absorption (%) | 77.207 | 79.391 | 36.377 | 69.407 |
| Skin permeability (log Kp) | −2.735 | −3.493 | −2.735 | −2.722 |
| P-gp substrate | Yes | Yes | Yes | No |
| VDss (log L/kg) | +1.559 | −0.985 | +0.581 | −1.098 |
| Fraction unbound | 0.206 | 0.242 | 0.658 | 0.529 |
| BBB permeability (log BB) | −1.098 | −0.886 | −1.407 | −0.647 |
| CNS permeability (log PS) | −3.065 | −2.249 | −3.856 | −2.608 |
| CYP1A2 inhibitor | Yes | Yes | No | No |
| Total clearance (log mL/min/kg) | 0.407 | 0.529 | 0.307 | 0.508 |
| AMES mutagenicity | No | Yes | No | No |
| hERG I inhibitor | No | No | No | No |
| hERG II inhibitor | No | No | No | No |
| Hepatotoxicity | No | No | No | No |
| Skin sensitisation | No | No | No | No |

Quercetin and kaempferol showed predicted skin permeability values of −2.735 and −3.493 log Kp, respectively. Chlorogenic acid and caffeic acid showed −2.735 and −2.722 log Kp. All four compounds were predicted negative for hepatotoxicity, skin sensitization and hERG I/II inhibition in the supplied dataset. Quercetin, kaempferol and chlorogenic acid were predicted as P-gp substrates, whereas caffeic acid was not. Quercetin and kaempferol were predicted as CYP1A2 inhibitors; chlorogenic acid and caffeic acid

were not. The most important computational safety alert was the positive AMES prediction for kaempferol.

**DISCUSSION:**

The combined docking results indicate a target-selective pattern. Quercetin and kaempferol generated stronger predicted affinities toward JAK3 than the tofacitinib reference within the supplied docking protocol, whereas finasteride retained the most favorable predicted affinity against SRD5A2. This suggests that the flavonoids may warrant further investigation as JAK3-directed research candidates, but the docking score alone cannot establish greater inhibitory potency than an approved/reference drug. [4, 14, 15]

The weaker SRD5A2 scores of the phytoconstituents relative to finasteride are consistent with a more modest computational signal for this target. Importantly, docking does not model the complete biochemical context of SRD5A2 catalysis, membrane environment, cofactor effects or conformational dynamics. Therefore, the present results should be framed as ligand–target hypotheses rather than proof of 5α-reductase inhibition. [13, 17]

The ADMET dataset provides useful prioritization information. Quercetin had the most favorable JAK3 docking score and was predicted negative for AMES mutagenicity, hepatotoxicity and skin sensitization. Kaempferol also scored strongly at JAK3 but carried a predicted AMES-positive alert. For a topical hair-growth program, skin permeability predictions should be interpreted cautiously because log Kp is model-derived and does not directly quantify delivery to the hair follicle or dermal papilla. [12, 14, 15, 16]

The current findings are relevant to a broader literature in which phytochemicals are being investigated as modulators of hair-follicle signaling and 5α-reductase-related pathways. Recent work specifically used computational screening of phytochemicals against 5α-reductase in hair-growth research, highlighting the need for follow-up mechanistic and experimental validation. [1–3,9,14–16]

**CONCLUSION:**

The integrated computational dataset identified quercetin (−9.147 kcal/mol) and kaempferol (−8.833 kcal/mol) as the strongest JAK3-scoring phytoconstituents, both more negative than tofacitinib (−8.140 kcal/mol) within the supplied protocol. For SRD5A2, finasteride (−7.797 kcal/mol) remained the strongest predicted binder, followed by quercetin and kaempferol. Chlorogenic acid and caffeic acid showed comparatively weaker scores for both targets. ADMET predictions were generally favorable for several endpoints, but kaempferol's AMES-positive prediction is an important computational alert. Overall, the study supports quercetin and kaempferol as candidates for further experimental investigation, particularly in relation to JAK3-associated hair-growth mechanisms, while emphasizing that docking and ADMET predictions do not establish efficacy or clinical safety.

**CONFLICT OF INTEREST:**

The authors declare that there is no conflict of interest.

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