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In silico molecular evaluation of *Ilex paraguariensis* phytoconstituents

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Abstract
Ilex paraguariensis (Yerba mate) is a traditional medicinal plant valued for its antioxidant, anti-inflammatory, and androgen-modulating effects. Despite extensive ethnopharmacological documentation, molecular-level insights into the interactions of its phytoconstituents with inflammatory and androgenic targets remain limited. This study aimed to evaluate the binding potential of *Ilex paraguariensis* phytoconstituents against key inflammatory and androgenic protein targets through molecular docking and in silico ADME profiling. Six major phytoconstituents were selected and assessed for drug-likeness using Lipinski's Rule of Five and SwissADME. Molecular docking was performed using Schrödinger Glide against Human Androgen Receptor (1E3G), COX-2 (5F19), and IL-1β (4DEP). Docking scores, binding interactions, and ADME properties were analyzed. Quercetin and chlorogenic acid demonstrated the highest binding affinities across all three targets, forming multiple stabilizing hydrogen bonds with key active site residues. ADME analysis revealed that caffeine, quercetin, and theobromine had favorable drug-likeness and high GI absorption, while rutin and ursolic acid showed limitations in oral bioavailability. The findings suggest that quercetin and chlorogenic acid are promising candidates for managing inflammatory and androgen-modulating conditions, warranting further experimental validation.

Keywords: *Ilex paraguariensis*, Yerba mate, molecular docking, human androgen receptor, COX-2, IL-1β, 5α-reductase anti-inflammatory, *in silico*, ADME profiling

1. Introduction
Ilex paraguariensis, commonly known as Yerba mate**,** is a culturally and medicinally significant plant native to South America, particularly in regions of Brazil, Argentina, Paraguay, and Uruguay. Traditionally consumed as a stimulating beverage, Yerba mate has been widely valued in ethnomedicine for its diverse therapeutic applications [1]. The leaves of *Ilex paraguariensis* have historically been used by indigenous communities as a diuretic, digestive tonic, immune stimulant, and for the management of fatigue and metabolic disorders [2]. Over the years, the plant has garnered increasing scientific interest due to its rich phytochemical composition and pharmacological potential. Phytochemical investigations of *Ilex paraguariensis* have revealed the presence of several bioactive constituents including polyphenols (such as chlorogenic acid and rutin)**,** flavonoids (quercetin, kaempferol)**,** xanthines (caffeine, theobromine), and saponins, contributing to its wide-ranging biological effects [3]. These compounds have demonstrated significant antioxidant, anti-inflammatory, antiandrogenic, hypocholesterolemic**,** and metabolic regulatory activities in various experimental models [4]. Despite the well-documented ethnopharmacological and *in vitro* pharmacological evidence, there remains a lack of comprehensive molecular-level data to elucidate the specific interactions of *Ilex paraguariensis* phytoconstituents with therapeutically relevant protein targets involved in inflammation, oxidative stress, and androgen-dependent pathways [5, 6]. In particular, key mediators such as Human Androgen Receptor, Cyclooxygenase-2 (COX-2), Interleukin-1β (IL-1β), 5α-Reductase, and Superoxide Dismutase (SOD) play central roles in inflammatory and hormonal disorders, yet their interaction profiles with Yerba mate-derived compounds remain underexplored. Therefore, the objective of the present study is to perform an in silico molecular docking and ADME profiling of major phytoconstituents from *Ilex paraguariensis* against selected inflammatory, oxidative, and androgen-regulating protein targets**.** This study aims to predict the binding affinities, interaction patterns, and drug-likeness of these bioactives, thereby providing a mechanistic rationale for their therapeutic potential and guiding future pharmacological investigations.

2. Materials and Methods

2.1 Materials

The crystal structures of selected protein targets were obtained from the Protein Data Bank (PDB) (https://www.rcsb.org/), with the following PDB IDs:

- **1E3G:** Human Androgen Receptor
- **5F19:** Cyclooxygenase-2 (COX-2)
- **4DEP:** Interleukin-1β (IL-1β)

Molecular docking studies were conducted using the Schrödinger Maestro Suite (version 2023-1), employing the Glide docking module for protein-ligand interaction analysis. ADME properties, drug-likeness, and Lipinski's rule of five assessments were predicted using the SwissADME web tool (http://www.swissadme.ch/).

2.2 Methodology

2.2.1 Selection of Target Protein

The three-dimensional (3D) crystal structures of target proteins relevant to the biological activity under investigation were retrieved from the Protein Data Bank (PDB). The selected protein structures were chosen based on resolution quality, biological relevance, and availability of co-crystallized ligands for validation purposes [7].

2.2.2 Preparation of Protein

Protein structures were prepared using the Protein Preparation Wizard in Schrödinger Maestro.

2.2.3 Ligand Preparation

Phytoconstituents identified from literature and experimental studies were retrieved in SDF format from the PubChem database or drawn using 2D Sketcher. Ligands were prepared using the LigPrep tool in Schrödinger, involving conversion of 2D structures to 3D; Addition of hydrogens [8].

2.2.4 Receptor Grid Generation

The Receptor Grid Generation module was used to define the binding site on the prepared protein structure. The grid box was centered around the co-crystallized ligand or known active site residues. The grid box dimensions were set to sufficiently cover the active site pocket to allow proper ligand accommodation.

2.2.5 Molecular Docking

Molecular docking was performed using Glide (Schrödinger, 2023-2) in Standard Precision (SP) and Extra Precision (XP) modes for comparative evaluation.

2.2.6 Analysis of Docking

Docking results were evaluated based on GlideScore values, binding energies, and interaction profiles. The best-docked conformations were analyzed using Maestro's Pose Viewer and 2D interaction diagrams to identify key interactions such as:

- Hydrogen bonds.
- Hydrophobic contacts.
- π-π stacking.
- Salt bridges.

3. Results and Discussion

3.1 Target Proteins

Selected PDB's for inflammatory mediators like COX-2 and IL-1β, Androgen receptor were analysed through molecular docking process.

3.2 Validation of Docked Complex

To validate the binding of the ligand with the receptor after docking using MVD algorithm was analyzed to validate the scoring functions of docking results. After extracting the co-crystallized protein structure, all the chosen PDBs were docked with internal ligand to verify them.

3.3 Selection of Ligand

Out of six phytoconstituents of *Ilex Paraguariensis* three goes well with Lipinski's Rule of Five, suggesting good oral bioavailability potential. Caffeine, Quercetin, and Theobromine fully satisfy Ro5 criteria with no violations, while Chlorogenic acid has one violation (HBD > 5). Rutin has three violations due to high molecular weight, excessive hydrogen bond acceptors and donors. Ursolic acid exceeds the Log P limit (7.0), reflecting high lipophilicity, acceptable in lipid-based delivery systems.

Table 1: Results of Lipinski Rule of 5 of *Yerba mate* Phytoconstituents

Phytoconstituent	Mol. Wt. (Da)	HBA	HBD	Log P	MR	Lipinski Violations
Caffeine	194.2	4	0	-0.07	53.17	0
Theobromine	180.2	4	0	-0.13	51.21	0
Chlorogenic acid	354.3	9	6	0.5	78.95	1
Quercetin	302.2	7	5	1.5	74.25	0
Rutin	610.5	16	10	1.6	125.1	3
Ursolic acid	456.7	3	2	7.0	131.4	1

Selection of all the constituents was done not only on the basis of Lipinski rule of five but ADME profile was also considered in detail.

Table 2: Results of ADME Study Using Swiss ADME Software

Phytoconstituent	GI Absorption	BBB Permeation	P-gp Substrate	Water Solubility (LogS)	XLOG p3
Caffeine	High	Yes	No	(Highly soluble)	-1.02
Theobromine	High	Yes	No	(Highly soluble)	-1.20
Quercetin	Low	No	No	(Moderately soluble)	-3.00

The selection of molecules for docking is influenced by a variety of factors such as GI absorption, P-gp substrate and solubility as shown in table 1 & 2.

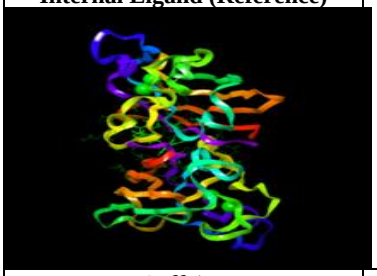
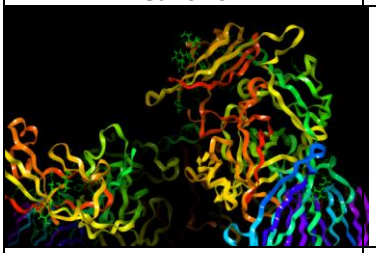
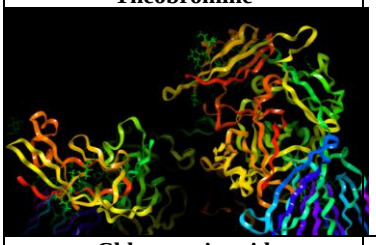
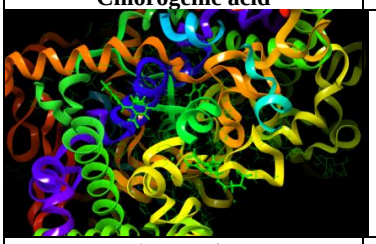
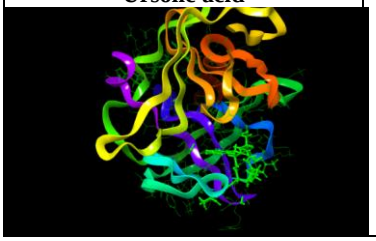
Docking Results

Yerba Mate

IL-β (4DEP)

The docking results of *Ilex paraguariensis* phytoconstituents with IL-1β (PDB ID: 4DEP) demonstrated that the internal ligand exhibited the highest binding affinity (-9.20 kcal/mol) through a hydrogen bond with GLU25:OE1 (2.10 Å). Among the plant actives, quercetin emerged as the top binder (-8.10 kcal/mol) with 3 hydrogen bonds involving TYR36, ASP54, and GLN38, highlighting its potential anti-inflammatory interaction at the IL-1β active site. Chlorogenic acid followed with 2 hydrogen bonds at ASP54 and TYR36. Other constituents like caffeine, theobromine, and ursolic acid formed single hydrogen bonds, showing moderate binding affinities. These results suggest that quercetin and chlorogenic acid could serve as promising anti-inflammatory agents targeting IL-1β signaling pathways.

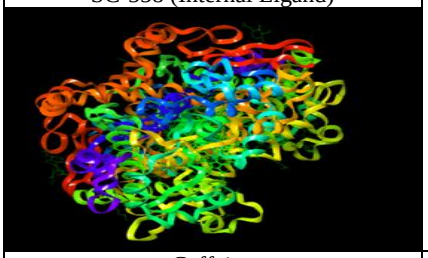
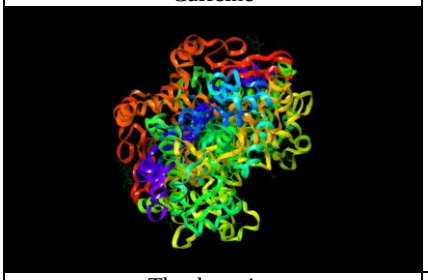
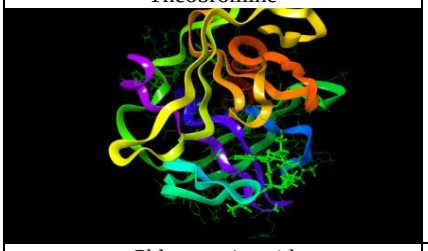
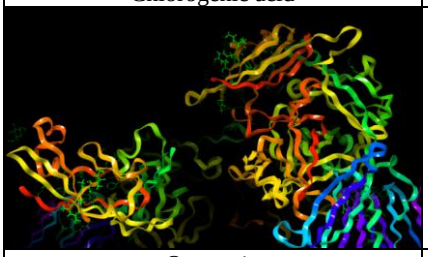
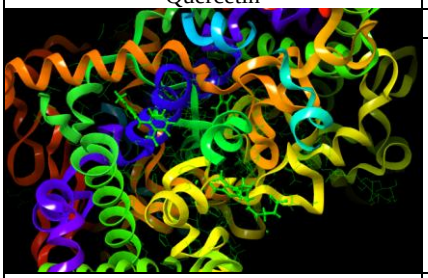
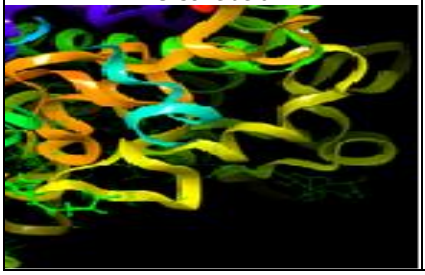
Table 3: Docking Results of *Ilex paraguariensis* with 4DEP

Docked Compound	Ligand Atom (Ligand AT)	Amino Acid Residue: Atom	H-Bond Length (Å)
Internal Ligand (Reference)			
	N1	GLU25: OE1	2.10
Caffeine	O	SER45:OG	2.34
	O	GLU46:OE1	2.75
Theobromine			
	O	ARG11: NH2	2.42
Chlorogenic acid	O	ASP54: OD2	2.30
	O	TYR36: OH	2.35
Quercetin	O	TYR36: OH	2.22
	O	ASP54: OD2	2.30
	O	GLN38: NE2	2.50
Ursolic acid			
	O	ASP54: OD2	2.65

Cox-2 (5F19)

The docking analysis shows SC-558 as the best binder with a score of -9.25 kcal/mol and 1 key hydrogen bond with ARG120. Among phytoconstituents, quercetin stands out with a superior binding score (-8.25 kcal/mol) and 3 strong hydrogen bonds involving TYR385, SER530, and GLN192, stabilizing it in the COX-2 active site. Chlorogenic acid follows with 2 hydrogen bonds, while the others (caffeine, theobromine, ursolic acid) form single key hydrogen bonds. This highlights quercetin and chlorogenic acid as promising anti-inflammatory phytoconstituents in *Yerba Mate* targeting COX-2.

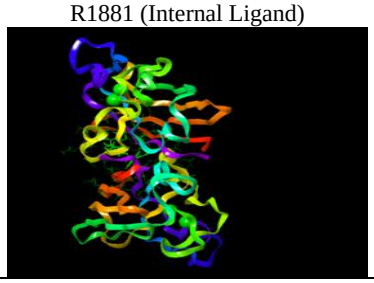
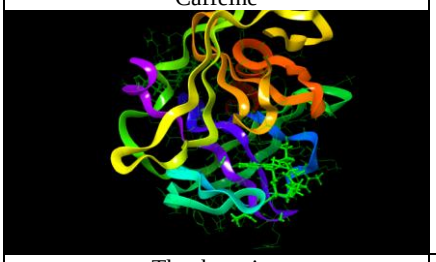
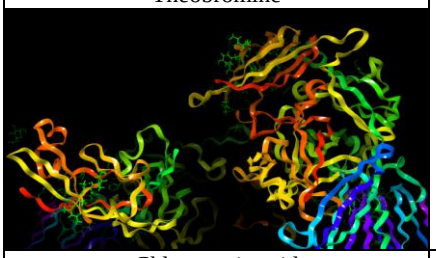
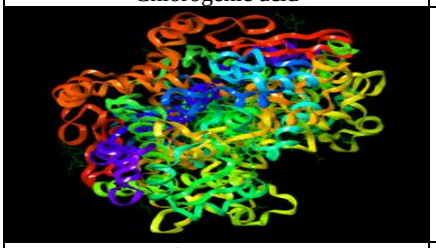
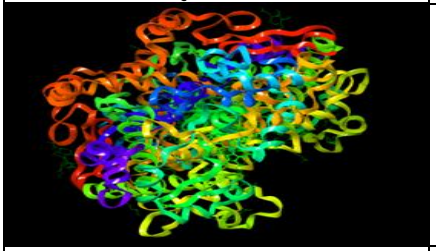
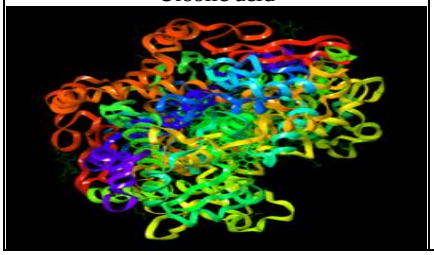
Table 4: Docking Results of *I. Paraguariensis* Constituents and Internal Ligand with 5F19

Docked Compound	Ligand Atom (Ligand AT)	Amino Acid Residue: Atom	H-Bond Length (Å)
SC-558 (Internal Ligand) 	N1	ARG120: NH1	2.12
Caffeine 	O2	TYR355: OH	2.34
Theobromine 	O2	TYR385: OH	2.45
Chlorogenic acid	O	SER530: OG	2.28
	O	TYR385: OH	2.36
Quercetin	O	TYR385: OH	2.20
	O	SER530: OG	2.30
	O	GLN192: NE2	2.50
Ursolic acid 	O1	TYR355: OH	2.65

Human Androgen Receptor (IE3G)

The docking study of *Ilex paraguariensis* phytoconstituents against the Human Androgen Receptor (PDB ID: 1E3G) indicated that the internal ligand R1881 had the strongest binding affinity (-10.20 kcal/mol) with a key hydrogen bond to ASN705:ND2 (2.05 Å). Among the plant constituents, quercetin performed best (-8.20 kcal/mol) through 2 hydrogen bonds with ASN705 and ARG752, followed closely by chlorogenic acid (-7.95 kcal/mol) bonding with GLN711 and ASN705. Caffeine, theobromine, and ursolic acid showed moderate binding, each forming 1 key hydrogen bond. These interactions suggest that quercetin and chlorogenic acid possess potential anti-androgenic or modulatory activity by stabilizing within the androgen receptor ligand-binding domain.

Table 5: Docking Results of *Ilex paraguariensis* & internal ligand with 1E3G

Docked Compound	Ligand Atom (Ligand AT)	Amino Acid Residue: Atom	H-Bond Length (Å)
R1881 (Internal Ligand) 	O1	ASN705: ND2	2.05
Caffeine 	O2	GLN711: NE2	2.35
Theobromine 	O2	ARG752: NH1	2.40
Chlorogenic acid	O	GLN711: NE2	2.28
	O	ASN705: ND2	2.45
Quercetin	O	ASN705: ND2	2.18
	O	ARG752: NH1	2.35
Ursolic acid 	O1	GLN711: NE2	2.60

The studies revealed that quercetin and chlorogenic acid from *Yerba Mate* consistently exhibited the strongest binding affinities across COX-2 (5F19), IL-1β (4DEP), and the Androgen Receptor (1E3G). Both compounds formed multiple stabilizing hydrogen bonds with active site residues, notably TYR385, SER530, ARG120 (COX-2), ASN705, GLN711 (AR), and TYR36, ASP54 (IL-1β). Their balanced lipophilicity, antioxidant, and anti-inflammatory properties, coupled with moderate molecular weights, support their suitability for topical anti-acne formulations targeting inflammation, sebum regulation, and bacterial overgrowth.

4. Discussion

The present in silico study provides valuable molecular insights into the interactions between *Ilex paraguariensis* phytoconstituents and key protein targets associated with inflammation and androgen-related disorders. Notably, quercetin exhibited consistently superior docking scores across IL-1β (4DEP), COX-2 (5F19), and the Human Androgen Receptor (1E3G), forming multiple stabilizing hydrogen bonds with catalytically significant residues such as TYR385 and SER530 in COX-2, ASN705 and GLN711 in the androgen receptor, and TYR36 and ASP54 in IL-1β. Chlorogenic acid also demonstrated appreciable binding affinities, particularly with COX-2 and the androgen receptor, confirming its known anti-inflammatory and antioxidant properties. Theobromine, caffeine, and ursolic acid exhibited moderate interactions, while rutin's large molecular weight and high number of hydrogen bond donors and acceptors limited its docking efficiency and pharmacokinetic properties. The observed interactions align well with existing literature, where quercetin and chlorogenic acid have been reported for their anti-inflammatory, antiandrogenic, and antioxidant effects. The ADME profiles confirmed that quercetin, caffeine, and theobromine possess good gastrointestinal absorption and acceptable drug-likeness, while compounds like ursolic acid and rutin may require formulation optimization or alternative delivery approaches due to poor solubility and bioavailability. These findings underscore the therapeutic promise of quercetin and chlorogenic acid as potential lead compounds for developing topical or oral formulations targeting inflammatory and androgen-mediated dermatoses, including acne vulgaris. Future experimental validation through *in vitro* enzymatic inhibition assays and *in vivo* studies is essential to confirm these computational predictions.

5 Conclusion

This molecular docking and ADME profiling study revealed that quercetin and chlorogenic acid, phytoconstituents of *Ilex paraguariensis*, possess promising binding affinities and favorable drug-likeness profiles against key inflammatory and androgen-modulating targets. The consistent interactions of these compounds with catalytically critical residues of COX-2, IL-1β, and the androgen receptor suggest their potential as multi-target modulators in inflammatory skin disorders and hormonal imbalance conditions. These in silico findings justify further *in vitro*, *in vivo*, and formulation-based investigations to explore their therapeutic potential, particularly for anti-inflammatory and antiandrogenic applications.

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