JOURNAL OF TROPICAL PHARMACY AND CHEMISTRY
https://jtpc.ff.unmul.ac.id
Volume 9.3

Research Article

Prediction of Bioactivity, Molecular Targets, and ADMET Properties of Chlorogenic Acid Derived from Coffee Beans (*Coffea liberica)*

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Abstract

Chlorogenic acid is a major polyphenolic compound present in coffee beans and has been widely recognized for its diverse pharmacological properties. However, comprehensive information regarding its bioactivity spectrum, molecular targets, and pharmacokinetic characteristics remains limited, particularly for chlorogenic acid derived from Coffea liberica. This study aimed to evaluate the bioactivity, molecular targets, and ADMET properties of chlorogenic acid using an integrated in silico approach. Bioactivity prediction was performed using the Way2Drug platform to identify potential pharmacological activities. Molecular target identification was conducted using SwissTargetPrediction to determine probable protein targets relevant to human biology. Pharmacokinetic and toxicity profiles were assessed using the pkCSM web server to evaluate absorption, distribution, metabolism, excretion, and toxicity parameters. The bioactivity analysis revealed strong predicted antioxidant, membrane-protective, anti-inflammatory, and anticarcinogenic activities. Target prediction indicated interactions with multiple protein classes, predominantly enzymes and proteases, including aldo-keto reductases, matrix metalloproteinases, carbonic anhydrases, and proteins associated with metabolic, inflammatory, oncogenic, and neurodegenerative pathways. ADMET analysis demonstrated moderate oral absorption, limited central nervous system penetration, low risk of cytochrome P450–mediated drug–drug interactions.

Keywords: Chlorogenic Acid, Coffea Liberica, In Silico Study, Molecular Target Prediction, ADMET

Accepted: 30 Oktober 2025
Approved: 30 November 2025
Publication: 24 Desember 2025

Citation: Y. Saristiana, F. Prasetyawan, M.W. Ariawan, L. Savitri, S. Musttaqin, Herman, "Prediction of Bioactivity, Molecular Targets, and ADMET Properties of Chlorogenic Acid Derived from Coffee Beans (*Coffea liberica*)", Journal of Tropical Pharmacy and Chemistry (JTPC), vol. 9, no. 3, pp. 282-293, Des. 2025, doi: 10.30872/jtpc.v9i3.318

Doi : 10.30872/jtpc.v9i3.318

1 Introduction

Chlorogenic acid is one of the most abundant polyphenolic compounds found in coffee beans and has attracted significant scientific interest due to its broad spectrum of biological activities. Coffee is one of the most widely consumed beverages worldwide, and its health benefits have been extensively investigated in recent decades. Among various coffee species, *Coffea liberica* is less studied compared to *Coffea arabica* and *Coffea canephora*, despite its unique phytochemical composition and increasing economic value [1].

The chemical constituents of coffee beans contribute substantially to their pharmacological properties. Chlorogenic acid, an ester of caffeic acid and quinic acid, is considered a major bioactive compound responsible for many of the health-promoting effects of coffee consumption [2]. Numerous studies have reported that chlorogenic acid exhibits antioxidant, anti-inflammatory, antidiabetic, antihypertensive, antimicrobial, and anticancer activities. These pharmacological effects make chlorogenic acid a promising candidate for drug discovery and development [3].

Biological activity of a compound is not solely determined by its chemical structure but also by its interaction with molecular targets in biological systems. Understanding the molecular targets of chlorogenic acid is crucial for elucidating its mechanism of action. Molecular target identification can provide insights into signaling pathways, enzyme inhibition, and receptor binding associated with therapeutic effects [4,5]. Despite extensive research on chlorogenic acid, comprehensive information regarding its molecular targets remains limited. Traditional experimental approaches for target identification are time-consuming, costly, and require extensive laboratory resources. Advances in computational biology have provided alternative strategies to predict bioactivity and molecular targets efficiently [6].

In silico approaches have become essential tools in modern pharmaceutical research. Computational prediction methods enable rapid screening of compounds and identification of potential biological targets. These approaches reduce experimental burden and accelerate early-stage drug discovery [7]. In addition to bioactivity and target interaction, the pharmacokinetic and toxicity profiles of compounds are critical for their therapeutic potential [8]. Absorption, distribution, metabolism, excretion, and toxicity, collectively known as ADMET properties, determine the safety and efficacy of drug candidates. Many promising bioactive compounds fail during clinical development due to unfavorable ADMET characteristics. Therefore, early evaluation of ADMET properties is essential to minimize late-stage drug failure. Chlorogenic acid, although widely consumed through dietary sources, requires systematic evaluation of its ADMET profile when considered for pharmaceutical applications. Natural compounds are often assumed to be safe, but this assumption may not always be accurate [9,10].

Computational ADMET prediction provides valuable insights into pharmacokinetic behavior and potential toxicity risks. In silico ADMET analysis allows researchers to assess oral bioavailability, intestinal absorption, blood–brain barrier permeability, metabolic stability, and toxicity parameters. Integrating bioactivity prediction, molecular target identification, and ADMET evaluation provides a holistic assessment of a compound's drug-likeness. The use of integrated computational approaches aligns with current trends in pharmacoinformatics and systems pharmacology [11]. *Coffea liberica* represents an underexplored source of bioactive compounds with potential therapeutic value. Investigating chlorogenic acid derived from *Coffea liberica* may reveal novel pharmacological insights distinct from other coffee species. The phytochemical diversity of *Coffea liberica* may influence the biological behavior of chlorogenic acid. Exploring species-specific bioactivity contributes to the rational utilization of natural resources [12,13].

The increasing global interest in plant-based therapeutics highlights the importance of scientific validation of traditional and dietary compounds. Chlorogenic acid has been associated with the modulation of oxidative stress, glucose metabolism, lipid metabolism, and inflammatory responses [14]. These biological processes are closely related to chronic diseases such as diabetes mellitus,

cardiovascular diseases, neurodegenerative disorders, and cancer. Identifying molecular targets involved in these pathways is essential for understanding the therapeutic relevance of chlorogenic acid. In silico target prediction tools use chemical similarity, machine learning algorithms, and bioactivity databases to predict potential protein targets [15,16]. Such tools have demonstrated reliability and efficiency in drug discovery research. Computational bioactivity prediction also supports hypothesis generation for future experimental validation. The integration of computational predictions with experimental studies enhances research efficiency and scientific rigor [17].

ADMET prediction tools provide early warnings of potential toxicity issues, such as hepatotoxicity, cardiotoxicity, or mutagenicity. Evaluating these parameters is particularly important when considering long-term use or high-dose formulations. Chlorogenic acid's widespread dietary exposure does not eliminate the need for pharmacokinetic evaluation in therapeutic contexts. Differences in dose, formulation, and route of administration can significantly alter ADMET behavior. Therefore, systematic in silico evaluation is justified and necessary [18,19]. The application of in silico methods aligns with ethical considerations by reducing reliance on animal testing. Computational approaches also support sustainable and cost-effective research practices [20]. Despite the growing body of literature on chlorogenic acid, comprehensive studies integrating bioactivity prediction, molecular target identification, and ADMET profiling remain scarce [21]. Most existing studies focus on isolated biological effects without exploring underlying molecular interactions or pharmacokinetic properties. This knowledge gap limits the translational potential of chlorogenic acid in drug development. Addressing this gap is essential for advancing chlorogenic acid from a dietary compound to a potential therapeutic agent. The present study aims to provide a comprehensive in silico assessment of chlorogenic acid derived from *Coffea liberica*. By integrating bioactivity prediction, molecular target analysis, and ADMET evaluation, this study seeks to generate systematic insights into its pharmacological potential [22,23].

The findings are expected to contribute to the scientific understanding of chlorogenic acid and support future experimental and clinical research. Furthermore, this study may serve as a reference for pharmacoinformatics-based evaluation of other natural compounds [24,25]. The results may also promote the utilization of *Coffea liberica* as a valuable source of bioactive compounds.

2 Method

This study employed an in silico research design to predict the bioactivity, molecular targets, and ADMET properties of chlorogenic acid derived from coffee beans (Coffea liberica). The overall workflow consisted of compound preparation, bioactivity prediction, molecular target identification, and pharmacokinetic and toxicity assessment using established computational platforms. Chlorogenic acid was selected as the compound of interest due to its high abundance in coffee beans and its reported pharmacological potential. The chemical structure of chlorogenic acid was obtained from publicly available chemical databases in canonical SMILES format to ensure compatibility with computational tools.

Structural verification was performed to confirm molecular integrity prior to analysis. The bioactivity prediction was conducted using the Way2Drug platform, which applies machine learning algorithms and curated bioactivity databases to predict the biological activity spectrum of small molecules. Way2Drug was utilized to estimate the probability of chlorogenic acid exhibiting specific pharmacological activities based on structural similarity and known ligand–target interactions. The predicted bioactivity profiles included potential therapeutic classes, mechanism-based activity predictions, and likelihood scores, which were used to identify the most relevant biological functions associated with chlorogenic acid. The use of Way2Drug allowed rapid and systematic screening of bioactive potential without the need for preliminary in vitro experiments.

Following bioactivity prediction, molecular target identification was performed using the SwissTargetPrediction web server. SwissTargetPrediction predicts potential protein targets of small molecules based on a combination of two-dimensional and three-dimensional chemical similarity with

Doi: 10.30872/jtpc.v9i3.318

known ligands. The SMILES structure of chlorogenic acid was uploaded to the SwissTargetPrediction platform, and the analysis was conducted with the species parameter set to Homo sapiens to ensure relevance to human pharmacology. The output included a ranked list of predicted protein targets along with probability scores reflecting the confidence of each prediction. Targets with higher probability values were considered more likely to interact with chlorogenic acid and were prioritized for further analysis. The predicted targets were classified according to protein families, such as enzymes, kinases, proteases, receptors, and transporters, to provide insight into potential mechanisms of action. This approach facilitated the identification of signaling pathways and biological processes potentially modulated by chlorogenic acid.

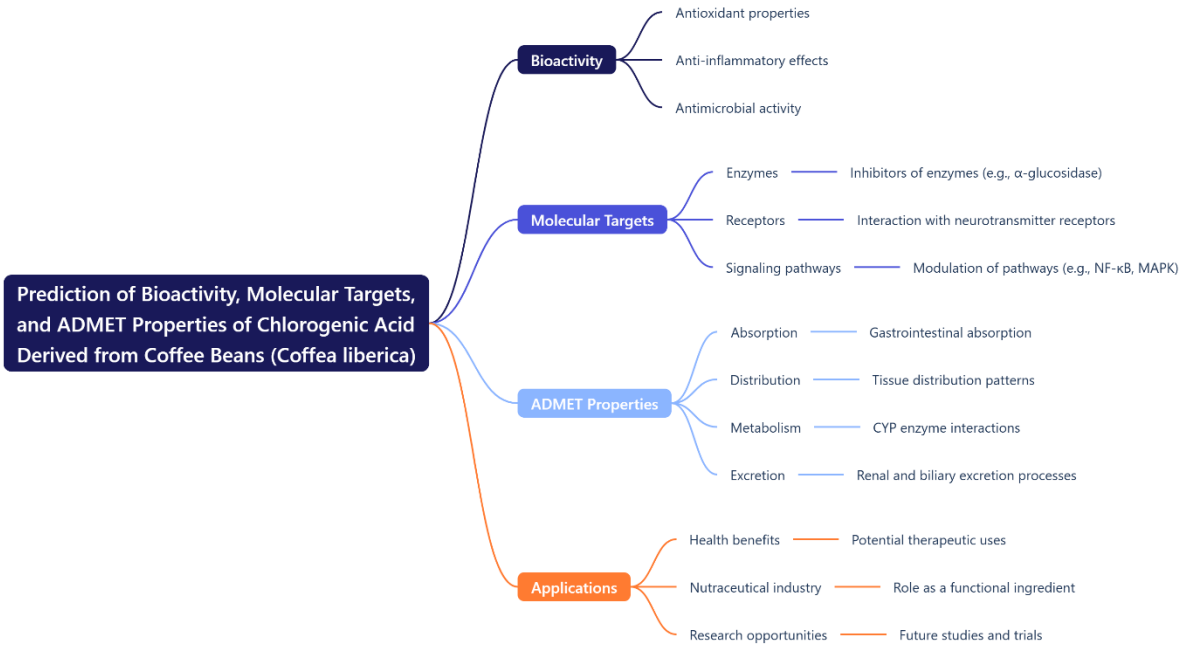

Figure 1. Mind Maps Reseach

The pharmacokinetic and toxicity properties of chlorogenic acid were evaluated using the pkCSM web-based platform. pkCSM predicts ADMET parameters using graph-based signatures derived from molecular structure. The SMILES representation of chlorogenic acid was input into the pkCSM server to assess key pharmacokinetic properties, including intestinal absorption, Caco-2 permeability, volume of distribution, blood–brain barrier permeability, and metabolic interactions with cytochrome P450 enzymes. Additionally, excretion-related parameters, such as total clearance and renal excretion, were predicted to evaluate elimination behavior. Toxicity prediction was also conducted using pkCSM to estimate potential adverse effects, including hepatotoxicity, cardiotoxicity (hERG inhibition), mutagenicity, and acute toxicity. The predicted ADMET data were interpreted in the context of drug-likeness and safety to assess the feasibility of chlorogenic acid as a therapeutic candidate.

All computational analyses were performed under default settings of each platform to maintain methodological consistency and reproducibility. The integration of bioactivity prediction, molecular target identification, and ADMET evaluation enabled a comprehensive pharmacoinformatics assessment of chlorogenic acid.

The combined use of Way2Drug, SwissTargetPrediction, and pkCSM provided complementary insights into biological activity, molecular mechanisms, and pharmacokinetic behavior. This integrated in silico methodology offers an efficient and ethical approach to early-stage drug discovery and supports the rational evaluation of natural compounds derived from Coffea liberica. The results obtained from this study are intended to serve as a predictive framework for subsequent experimental validation and further pharmacological investigation.

3 Result and Discussion

3.1 Predicted Biological Activities of Chlorogenic Acid Bioactivity

The predicted bioactivity profile of chlorogenic acid demonstrates a broad and diverse spectrum of biological activities, indicating its potential as a multi-target bioactive compound

Table 1. Predicted Bioactivity Profile of Chlorogenic Acid

No.	Pa (Probability Active)	Pi (Probability Inactive)	Predicted Activity
1	0.940	0.004	Membrane integrity agonist
2	0.920	0.001	Choleretic
3	0.865	0.004	Membrane permeability inhibitor
4	0.856	0.002	Free radical scavenger
5	0.855	0.003	Lipid peroxidase inhibitor
6	0.846	0.004	Oxidoreductase inhibitor
7	0.846	0.004	Anticarcinogenic
8	0.833	0.003	Chemopreventive
9	0.826	0.010	HIF1A expression inhibitor
10	0.815	0.003	Phosphatase inhibitor
11	0.808	0.017	Antieczematic
12	0.785	0.004	Antioxidant
13	0.778	0.014	Antineoplastic
14	0.771	0.015	Feruloyl esterase inhibitor
15	0.769	0.004	Proliferative diseases treatment
16	0.752	0.034	Mucomembranous protector
17	0.750	0.001	Quinate 5-dehydrogenase inhibitor
18	0.726	0.006	Antihypoxic
19	0.716	0.021	G-protein-coupled receptor kinase inhibitor
20	0.716	0.021	Beta-adrenergic receptor kinase inhibitor
21	0.707	0.014	UDP-glucuronosyltransferase substrate
22	0.705	0.053	CDP-glycerol glycerophosphotransferase inhibitor
23	0.701	0.003	4-Coumarate-CoA ligase inhibitor

The high Pa values observed across numerous activities suggest a strong likelihood of pharmacological relevance. The highest predicted activity was observed for membrane integrity agonist activity, with a Pa value of 0.940 and a very low Pi value of 0.004. This result indicates that chlorogenic acid may play a significant role in maintaining or enhancing cellular membrane stability, which is essential for protecting cells against oxidative stress, inflammatory damage, and cytotoxic agents. Membrane integrity is a crucial determinant of cell survival, and compounds that stabilize membranes are often associated with cytoprotective and anti-inflammatory effects. This finding aligns with previous reports describing the protective effects of chlorogenic acid on cellular structures under oxidative conditions.

Choleretic activity also exhibited a high Pa value of 0.920, suggesting a strong probability that chlorogenic acid may stimulate bile production or secretion. Choleretic agents are important for supporting liver function, enhancing lipid digestion, and promoting detoxification processes. This prediction supports existing evidence indicating the hepatoprotective potential of chlorogenic acid and its role in modulating lipid metabolism. The predicted choleretic effect may also contribute to the prevention of metabolic disorders, particularly those associated with dyslipidemia and non-alcoholic fatty liver disease.

The prediction of membrane permeability inhibitor activity (Pa = 0.865) further reinforces the membrane-stabilizing properties of chlorogenic acid. By limiting excessive membrane permeability,

chlorogenic acid may protect cells from toxic insults and prevent the uncontrolled influx of harmful substances. This activity is closely related to its antioxidant and cytoprotective roles and may explain its protective effects in various pathological conditions. The presence of multiple membrane-related activities highlights the importance of chlorogenic acid in preserving cellular homeostasis.

Free radical scavenging activity showed a high Pa value of 0.856, confirming the well-documented antioxidant properties of chlorogenic acid. Free radical scavengers neutralize reactive oxygen species, thereby reducing oxidative damage to lipids, proteins, and nucleic acids. This activity is particularly relevant in the context of chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and cancer, where oxidative stress plays a central pathogenic role. The antioxidant activity is further supported by the prediction of lipid peroxidase inhibitor activity (Pa = 0.855), indicating that chlorogenic acid may prevent lipid oxidation within cellular membranes. Inhibition of lipid peroxidation is critical for maintaining membrane fluidity and function, as well as preventing the formation of toxic lipid peroxides.

Oxidoreductase inhibitor activity (Pa = 0.846) suggests that chlorogenic acid may modulate redox-related enzymes involved in oxidative metabolism. Oxidoreductases play key roles in cellular respiration, detoxification, and redox signaling. By inhibiting certain oxidoreductases, chlorogenic acid may influence oxidative stress pathways and energy metabolism. This activity may also contribute to its anti-inflammatory and anticancer properties by regulating redox-sensitive signaling pathways.

The prediction of anticarcinogenic activity (Pa = 0.846) and chemopreventive activity (Pa = 0.833) indicates a strong potential role of chlorogenic acid in cancer prevention. Anticarcinogenic compounds reduce the initiation, promotion, or progression of cancer, while chemopreventive agents interfere with carcinogenesis at early stages. These predictions are consistent with experimental studies demonstrating that chlorogenic acid can inhibit tumor growth, induce apoptosis, and suppress metastasis in various cancer models. The combination of antioxidant, anti-inflammatory, and enzyme inhibitory activities may underlie its chemopreventive effects. Inhibition of hypoxia-inducible factor 1-alpha (HIF1A) expression (Pa = 0.826) represents a particularly important finding. HIF1A is a key transcription factor involved in cellular adaptation to hypoxia and plays a critical role in tumor angiogenesis, metabolism, and survival. Inhibition of HIF1A expression suggests that chlorogenic acid may interfere with hypoxia-driven cancer progression and angiogenesis. This activity further supports its predicted antineoplastic and anticancer potential.

Phosphatase inhibitor activity (Pa = 0.815) indicates that chlorogenic acid may regulate phosphorylation-dependent signaling pathways. Protein phosphatases are involved in controlling cell growth, differentiation, and apoptosis. Modulation of phosphatase activity can significantly impact cellular signaling networks, including those associated with inflammation and cancer. This finding suggests that chlorogenic acid may exert regulatory effects on multiple intracellular signaling cascades.

Antieczematic activity (Pa = 0.808) suggests potential benefits of chlorogenic acid in inflammatory skin conditions. Eczema is characterized by inflammation, oxidative stress, and impaired skin barrier function. The predicted antieczematic effect may be attributed to the compound's antioxidant, anti-inflammatory, and membrane-stabilizing properties. This finding highlights the potential application of chlorogenic acid in dermatological formulations. Antioxidant activity (Pa = 0.785), although slightly lower than free radical scavenging activity, further confirms the compound's strong redox-modulating capacity. The presence of multiple antioxidant-related predictions indicates that chlorogenic acid may act through several complementary mechanisms to reduce oxidative stress. This redundancy enhances its potential efficacy in complex biological systems.

The prediction of antineoplastic activity (Pa = 0.778) and proliferative diseases treatment (Pa = 0.769) suggests that chlorogenic acid may inhibit abnormal cell proliferation. These activities support its potential role in managing diseases characterized by uncontrolled cell growth, including cancer and hyperproliferative disorders. The relatively high Pa values indicate a meaningful likelihood of therapeutic relevance.

Enzyme-specific activities, such as feruloyl esterase inhibitor (Pa = 0.771) and quinate 5-dehydrogenase inhibitor (Pa = 0.750), reflect the ability of chlorogenic acid to interact with metabolic enzymes. These enzymes are involved in phenolic compound metabolism and energy pathways, suggesting that chlorogenic acid may influence metabolic processes at the enzymatic level. Such interactions may contribute to its biological effects in both microbial and mammalian systems. Antihypoxic activity (Pa = 0.726) suggests that chlorogenic acid may improve cellular tolerance to low oxygen conditions. This activity is particularly relevant in ischemic diseases and tumor microenvironments. Combined with HIF1A inhibition, this finding indicates a complex role of chlorogenic acid in modulating hypoxia-related pathways.

Mucomembranous protector activity (Pa = 0.752) suggests a protective effect on mucosal membranes, which may be beneficial in gastrointestinal disorders. This activity aligns with the compound's membrane-stabilizing and antioxidant properties and supports its potential use in gastrointestinal protection. The predicted inhibition of G-protein-coupled receptor kinase and beta-adrenergic receptor kinase (Pa = 0.716) indicates possible modulation of GPCR signaling pathways. GPCR kinases regulate receptor desensitization and signaling duration, and their inhibition may influence cardiovascular, metabolic, and neurological functions. This activity suggests a potential regulatory role of chlorogenic acid in receptor-mediated signaling.

The prediction that chlorogenic acid may act as a UDP-glucuronosyltransferase substrate (Pa = 0.707) is relevant for its metabolic fate. UDP-glucuronosyltransferases are key enzymes involved in phase II metabolism and drug clearance. Being a substrate for these enzymes suggests that chlorogenic acid may undergo glucuronidation, influencing its bioavailability and elimination. Finally, the predicted inhibition of CDP-glycerol glycerophosphotransferase (Pa = 0.705) and 4-coumarate-CoA ligase (Pa = 0.701) reflects additional enzymatic interactions related to lipid and phenylpropanoid metabolism. Although these activities have slightly lower Pa values, they still indicate a moderate probability of biological relevance and contribute to the overall multi-target profile of chlorogenic acid.

Predicted Target Class *of* Chlorogenic Acid

The molecular target prediction results indicate that chlorogenic acid interacts with a diverse set of protein targets, predominantly enzymes, proteases, and lyases, suggesting a multi-target pharmacological profile. The dominance of enzyme-related targets reflects the strong potential of chlorogenic acid to modulate metabolic and biochemical pathways.

Table 2. Predicted Molecular Targets and Target Classes of Chlorogenic Acid

No.	Target	Target Class
1	Aldo-keto reductase family 1 member B10 (AKR1B10)	Enzyme
2	Aldose reductase (AKR1B1)	Enzyme
3	Matrix metalloproteinase 13 (MMP13)	Protease
4	Matrix metalloproteinase 2 (MMP2)	Protease
5	Matrix metalloproteinase 12 (MMP12)	Protease
6	Beta amyloid A4 protein (APP)	Membrane receptor
7	Beta-secretase 1 (BACE1)	Protease
8	Carbonic anhydrase I (CA1)	Lyase
9	Carbonic anhydrase II (CA2)	Lyase
10	Carbonic anhydrase IX (CA9)	Lyase
11	Carbonic anhydrase VB (CA5B)	Lyase
12	Carbonic anhydrase XII (CA12)	Lyase
13	Endothelin receptor ETA (EDNRA)	Family A G protein-coupled receptor
14	Glucose-6-phosphate translocase (SLC37A4)	Electrochemical transporter
15	Leukocyte elastase (ELANE)	Protease

The predicted targets, members of the aldo-keto reductase family, particularly AKR1B10 and AKR1B1, were identified as prominent enzyme targets. Aldo-keto reductases play critical roles in glucose metabolism, detoxification of aldehydes, and oxidative stress regulation. Inhibition of aldose reductase (AKR1B1) has been widely recognized as a therapeutic strategy for preventing diabetic complications, including neuropathy, retinopathy, and nephropathy. The predicted interaction between chlorogenic acid and AKR1B1 supports its reported antidiabetic and antioxidant effects. Similarly, AKR1B10 is involved in carcinogenesis and cellular proliferation, particularly in liver and lung cancers. Modulation of AKR1B10 activity by chlorogenic acid may contribute to its predicted anticarcinogenic and chemopreventive activities observed in the bioactivity analysis.

Matrix metalloproteinases (MMPs), including MMP2, MMP12, and MMP13, were also identified as key protease targets. MMPs are zinc-dependent endopeptidases responsible for extracellular matrix remodeling, tissue repair, and inflammatory responses. Dysregulated MMP activity is strongly associated with cancer invasion, metastasis, chronic inflammation, and tissue degradation. The predicted inhibition of MMPs by chlorogenic acid suggests a potential mechanism underlying its antineoplastic and anti-inflammatory properties. In particular, MMP2 and MMP13 are known to facilitate tumor cell migration and invasion, while MMP12 is implicated in inflammatory lung diseases and atherosclerosis. The ability of chlorogenic acid to interact with these proteases supports its potential role in suppressing pathological tissue remodeling and tumor progression.

Beta-amyloid A4 protein (APP) and beta-secretase 1 (BACE1) were predicted as additional targets, indicating possible neuroprotective effects of chlorogenic acid. APP processing by BACE1 leads to the formation of amyloid-beta peptides, which accumulate in the brains of patients with Alzheimer's disease. Inhibition of BACE1 is considered a major therapeutic approach in Alzheimer's disease research. The predicted interaction of chlorogenic acid with APP and BACE1 suggests that it may modulate amyloidogenic pathways and reduce amyloid-beta formation. This finding aligns with previous reports demonstrating the neuroprotective and antioxidant effects of chlorogenic acid and highlights its potential relevance in neurodegenerative disorders.

A notable cluster of predicted targets belongs to the carbonic anhydrase (CA) family, including CA1, CA2, CA9, CA5B, and CA12. Carbonic anhydrases are lyase enzymes that catalyze the reversible hydration of carbon dioxide and play essential roles in pH regulation, respiration, electrolyte balance, and tumor microenvironment adaptation. CA9 and CA12, in particular, are overexpressed in hypoxic tumor tissues and are associated with tumor growth, invasion, and resistance to therapy. The predicted interaction between chlorogenic acid and tumor-associated carbonic anhydrases suggests a potential anticancer mechanism through modulation of tumor acidity and hypoxia adaptation. Inhibition of CA enzymes may disrupt cancer cell survival under hypoxic conditions, complementing the predicted HIF1A expression inhibition observed in the bioactivity analysis.

The identification of endothelin receptor ETA (EDNRA) as a predicted target suggests potential cardiovascular and vascular regulatory effects of chlorogenic acid. Endothelin receptors are G protein-coupled receptors involved in vasoconstriction, blood pressure regulation, and vascular remodeling. Modulation of EDNRA activity may contribute to the antihypertensive and cardioprotective effects associated with chlorogenic acid consumption. This finding is consistent with epidemiological studies linking coffee polyphenols to improved vascular function and reduced cardiovascular risk.

Glucose-6-phosphate translocase (SLC37A4) was predicted as a transporter target, indicating a possible role of chlorogenic acid in glucose homeostasis. SLC37A4 is involved in glucose-6-phosphate transport within the endoplasmic reticulum and plays a role in glucose metabolism and glycogen storage. Interaction with this transporter may further support the antidiabetic potential of chlorogenic acid by influencing hepatic glucose production and metabolic regulation.

Leukocyte elastase (ELANE), a serine protease involved in inflammatory responses and tissue damage, was also identified as a predicted target. Excessive ELANE activity is associated with chronic inflammatory diseases, lung tissue injury, and cardiovascular disorders. The predicted interaction between chlorogenic acid and ELANE suggests an anti-inflammatory mechanism that may contribute

to tissue protection and immune regulation. This activity complements the membrane-stabilizing and antioxidant bioactivities identified in the Way2Drug analysis.

Overall, the predicted molecular targets of chlorogenic acid demonstrate strong coherence with its bioactivity profile. The convergence of enzyme inhibition, protease modulation, receptor interaction, and transporter targeting highlights the pleiotropic nature of chlorogenic acid. The integration of target prediction with bioactivity analysis suggests that chlorogenic acid exerts its pharmacological effects through multiple interconnected pathways, including oxidative stress regulation, metabolic modulation, inflammation control, cancer-related signaling, and neuroprotection. This multi-target profile is particularly advantageous for managing complex chronic diseases that involve dysregulated networks rather than single molecular defects.

From a drug discovery perspective, the dominance of enzymatic and proteolytic targets suggests that chlorogenic acid may serve as a lead compound or pharmacophore for the development of multi-target therapeutics. However, the predicted interactions require experimental validation through in vitro enzyme assays, molecular docking, and cellular studies to confirm binding affinity and functional effects. Nevertheless, the present in silico findings provide a strong scientific rationale for further pharmacological investigation and support the therapeutic potential of chlorogenic acid derived from *Coffea liberica*.

3.2 Predicted Target Class of Dexamethasone Bioactivity

The predicted ADMET profile of chlorogenic acid provides essential insights into its pharmacokinetic behavior and safety, which are critical factors for evaluating its potential as a therapeutic agent.

Table 3. Predicted ADMET Properties of Chlorogenic Acid (pkCSM Analysis)

No.	ADMET Category	Property	Predicted Value	Unit
Absorption				
1	Absorption	Water solubility	−2.449	log mol/L
2	Absorption	Caco-2 permeability	−0.840	log Papp (10^{-6} cm/s)
3	Absorption	Intestinal absorption (human)	36.377	% absorbed
4	Absorption	Skin permeability	−2.735	log Kp
5	Absorption	P-glycoprotein substrate	Yes	Categorical
6	Absorption	P-glycoprotein I inhibitor	No	Categorical
7	Absorption	P-glycoprotein II inhibitor	No	Categorical
Distribution				
8	Distribution	Volume of distribution (VDss, human)	0.581	log L/kg
9	Distribution	Fraction unbound (human)	0.658	Fu
10	Distribution	Blood–brain barrier permeability	−1.407	log BB
11	Distribution	CNS permeability	−3.856	log PS
Metabolism				
12	Metabolism	CYP2D6 substrate	No	Categorical
13	Metabolism	CYP3A4 substrate	No	Categorical
14	Metabolism	CYP1A2 inhibitor	No	Categorical

15	Metabolism	CYP2C19 inhibitor	No	Categorical
16	Metabolism	CYP2C9 inhibitor	No	Categorical
17	Metabolism	CYP2D6 inhibitor	No	Categorical
18	Metabolism	CYP3A4 inhibitor	No	Categorical
Excretion				
19	Excretion	Total clearance	0.307	log mL/min/kg
20	Excretion	Renal OCT2 substrate	No	Categorical
Toxicity				
21	Toxicity	AMES toxicity	No	Categorical
22	Toxicity	Maximum tolerated dose (human)	−0.134	log mg/kg/day
23	Toxicity	hERG I inhibitor	No	Categorical
24	Toxicity	hERG II inhibitor	No	Categorical
25	Toxicity	Oral rat acute toxicity (LD_{50})	1.973	mol/kg
26	Toxicity	Oral rat chronic toxicity (LOAEL)	2.982	log mg/kg_bw/day
27	Toxicity	Hepatotoxicity	No	Categorical
28	Toxicity	Skin sensitisation	No	Categorical
29	Toxicity	*Tetrahymena pyriformis* toxicity	0.285	log µg/L
30	Toxicity	Minnow toxicity	5.741	log mM

The absorption parameters indicate moderate aqueous solubility, as reflected by a water solubility value of −2.449 log mol/L. This level of solubility suggests that chlorogenic acid can dissolve sufficiently in physiological fluids, although its solubility may still pose limitations for high-dose oral formulations. The predicted Caco-2 permeability value of −0.840 log Papp indicates low intestinal epithelial permeability, which is consistent with the polar nature and multiple hydroxyl groups of chlorogenic acid. This limited permeability likely contributes to the moderate predicted human intestinal absorption of 36.377%, indicating that only a fraction of the orally administered compound may reach systemic circulation. Such absorption characteristics are common among polyphenolic compounds and suggest that formulation strategies or delivery systems may be required to enhance bioavailability.

The predicted skin permeability value of −2.735 log Kp indicates low transdermal penetration, suggesting that chlorogenic acid is unlikely to readily cross the skin barrier. This finding implies that topical formulations may require penetration enhancers to achieve therapeutic concentrations in deeper skin layers. The prediction that chlorogenic acid is a substrate of P-glycoprotein further supports the possibility of limited oral bioavailability. P-glycoprotein acts as an efflux transporter that can reduce intracellular drug accumulation by actively transporting substrates back into the intestinal lumen. However, the absence of P-glycoprotein inhibitory activity indicates that chlorogenic acid is unlikely to interfere with the pharmacokinetics of co-administered drugs through P-glycoprotein inhibition, thereby reducing the risk of transporter-mediated drug–drug interactions.

Distribution parameters suggest a moderate volume of distribution, as indicated by a VDss value of 0.581 log L/kg. This suggests that chlorogenic acid is distributed beyond the plasma compartment but does not extensively accumulate in tissues. The relatively high fraction unbound value of 0.658 indicates that a significant proportion of chlorogenic acid remains free in plasma, which may facilitate interaction with molecular targets. However, free drug is also more readily eliminated, which may contribute to a shorter systemic exposure. The predicted blood–brain barrier permeability (log BB = −1.407) and CNS permeability (log PS = −3.856) values indicate poor penetration into the central nervous system. These findings suggest that chlorogenic acid is unlikely to exert direct pharmacological

effects within the brain under normal systemic exposure conditions. While this limits its application for central nervous system disorders, it may also reduce the risk of CNS-related adverse effects.

Metabolism prediction results indicate that chlorogenic acid is neither a substrate nor an inhibitor of major cytochrome P450 enzymes, including CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2. This metabolic profile is highly favorable from a drug development perspective, as it suggests a low likelihood of metabolic drug–drug interactions. The absence of CYP inhibition implies that chlorogenic acid is unlikely to alter the metabolism of concurrently administered medications. Additionally, the lack of CYP substrate properties suggests that its metabolism may occur through alternative pathways, such as phase II conjugation reactions, which is consistent with the predicted interaction with UDP-glucuronosyltransferases observed in target prediction analyses.

Excretion parameters indicate a moderate total clearance value of 0.307 log mL/min/kg, suggesting that chlorogenic acid may be eliminated at a reasonable rate from the body. The prediction that chlorogenic acid is not a renal OCT2 substrate indicates that active renal tubular secretion via OCT2 is unlikely to play a major role in its elimination. These findings suggest that elimination may occur through a combination of renal filtration and hepatic metabolism, primarily via conjugation pathways.

The toxicity profile of chlorogenic acid is notably favorable. The absence of predicted AMES toxicity indicates a low risk of mutagenicity, which is an essential requirement for long-term therapeutic use. The predicted maximum tolerated dose in humans (−0.134 log mg/kg/day) suggests acceptable tolerability at pharmacologically relevant doses. Importantly, chlorogenic acid was not predicted to inhibit hERG I or hERG II channels, indicating a low risk of cardiotoxicity related to QT interval prolongation. Cardiotoxicity is a major cause of drug attrition, and the absence of hERG inhibition significantly enhances the safety profile of chlorogenic acid.

The predicted oral rat acute toxicity (LD_{50} = 1.973 mol/kg) and chronic toxicity (LOAEL = 2.982 log mg/kg_bw/day) indicate relatively low acute and chronic toxicity. These values suggest that chlorogenic acid has a wide safety margin, consistent with its long history of dietary exposure through coffee consumption. The absence of predicted hepatotoxicity further supports its hepatic safety, which is particularly important given the liver's central role in drug metabolism. Additionally, the lack of predicted skin sensitization suggests that chlorogenic acid may be suitable for topical applications with minimal risk of allergic reactions.

Ecotoxicity predictions, including *Tetrahymena pyriformis* and minnow toxicity, indicate low environmental toxicity at relevant concentrations. While these parameters are not directly related to human safety, they provide additional information regarding the environmental impact of chlorogenic acid and support its overall favorable safety profile. The predicted ADMET properties of chlorogenic acid reveal a compound with moderate oral absorption, limited CNS penetration, minimal risk of drug–drug interactions, and a strong safety profile. These characteristics are consistent with many bioactive dietary polyphenols and suggest that chlorogenic acid may be best suited for systemic applications targeting peripheral tissues or for use as a nutraceutical. The main limitation identified is its moderate bioavailability, which may be addressed through formulation optimization, such as nanoparticle delivery systems, prodrug strategies, or combination with absorption enhancers. Taken together, the ADMET analysis supports the further development of chlorogenic acid as a safe and promising bioactive compound, particularly for applications related to metabolic disorders, inflammation, and cancer prevention.

4. Conclusion

This study provides a comprehensive in silico evaluation of chlorogenic acid derived from Coffea liberica by integrating bioactivity prediction, molecular target identification, and ADMET profiling. The bioactivity analysis revealed that chlorogenic acid exhibits a broad spectrum of predicted biological activities, with dominant antioxidant, membrane-protective, anti-inflammatory, and anticarcinogenic properties. These activities support its potential role as a pleiotropic bioactive compound capable of

modulating multiple pathological processes. Molecular target prediction further demonstrated that chlorogenic acid interacts with a diverse range of protein targets, predominantly enzymes, proteases, and lyases, including aldo-keto reductases, matrix metalloproteinases, carbonic anhydrases, and key proteins involved in metabolic, inflammatory, oncogenic, and neurodegenerative pathways. The convergence of these targets with the predicted bioactivities highlights coherent mechanistic pathways underlying the therapeutic potential of chlorogenic acid.

The ADMET analysis revealed a favorable pharmacokinetic and safety profile, characterized by moderate oral absorption, limited central nervous system penetration, low risk of cytochrome P450–mediated drug–drug interactions, and absence of major toxicity signals, including mutagenicity, cardiotoxicity, and hepatotoxicity. Although the predicted bioavailability may be moderate due to limited permeability and P-glycoprotein efflux, the overall safety and metabolic stability suggest that chlorogenic acid is well suited for further development as a therapeutic or nutraceutical agent targeting peripheral tissues. Collectively, these findings support chlorogenic acid as a promising multi-target compound and provide a strong scientific basis for subsequent experimental validation, formulation optimization, and translational studies aimed at harnessing its pharmacological potential.

5. Bibliography

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