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In silico study of the antidiabetic potential of chlorogenic acid and caffeine from coffea canephora using network pharmacology and molecular docking

Kajian In Silico Potensi Antidiabetes Asam Klorogenat dan Kafein dari Coffea canephora melalui Network Pharmacology dan Molecular Docking

Erlidawati Erlidawati[1*] Rizarullah Rizarullah[2*], Rahmad Rizki Fazli[1], Shafa Mulyana[1]

[1]Chemistry Department, FKIP, Universitas Syiah Kuala, Darussalam, Banda Aceh, Indonesia

[2]Department of Biochemistry, Faculty of Medicine, Universitas Abulyatama, Aceh Besar, Indonesia

*Email: rizarullah_fk@abulyatama.ac.id

ABSTRACT

Background: *Type 2 diabetes mellitus (T2DM) is a global health challenge requiring safer and more effective therapies. Coffea canephora contains chlorogenic acid and caffeine, which have reported antidiabetic potential; however, their molecular mechanisms remain unclear.*

Objective: *To identify candidate targets and explore mechanisms relevant to T2DM for chlorogenic acid and caffeine from Coffea canephora through integrated network pharmacology and molecular docking.*

Methods: *Drug likeness was assessed using SwissADME. Target prediction, protein interaction network analysis, and functional enrichment analysis were performed to prioritize candidate targets associated with T2DM. Molecular docking was subsequently conducted to assess predicted binding affinities and characterize ligand interactions with the selected proteins. Docking results were compared with those of the respective reference ligands.*

Results: *Network pharmacology prioritized AKR1B1 for chlorogenic acid and ADORA2B for caffeine. Functional enrichment identified significant associations with insulin signaling, glucagon signaling, carbohydrate metabolism, and inflammatory pathways. Chlorogenic acid yielded a docking score of −8.74 kcal/mol against AKR1B1, compared with −10.10 kcal/mol for lidorestat, and formed favorable interactions with binding site residues. Caffeine yielded a less favorable docking score against ADORA2B (−4.82 kcal/mol) than BAY 60-6583 (−7.08 kcal/mol), with fewer critical interactions.*

Conclusion: *Chlorogenic acid and caffeine exhibited less favorable docking scores than their respective reference ligands. These findings identify potential interactions with proteins relevant to T2DM but do not establish biological activity or therapeutic efficacy. Experimental validation is required to confirm target engagement and functional effects. This study supports computational approaches for prioritizing natural compounds and generating mechanistic hypotheses for antidiabetic drug discovery.*

Keywords: *caffeine, chlorogenic acid, coffea canephora, molecular docking, network pharmacology, type 2 diabetes mellitus*

ABSTRAK

Latar Belakang: Diabetes mellitus tipe 2 (DMT2) merupakan tantangan kesehatan global yang membutuhkan terapi yang lebih aman dan efektif. Coffea canephora mengandung asam klorogenat dan kafein, yang dilaporkan memiliki potensi antidiabetes; namun, mekanisme molekulernya masih belum jelas.

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Tujuan: Untuk mengidentifikasi target kandidat dan mengeksplorasi mekanisme yang relevan dengan DMT2 untuk asam klorogenat dan kafein dari Coffea canephora melalui farmakologi jaringan terintegrasi dan docking molekuler.
Metode: Kemiripan obat dinilai menggunakan SwissADME. Prediksi target, analisis jaringan interaksi protein, dan analisis pengayaan fungsional dilakukan untuk memprioritaskan target kandidat yang terkait dengan T2DM. Docking molekuler kemudian dilakukan untuk menilai afinitas ikatan yang diprediksi dan mengkarakterisasi interaksi ligan dengan protein yang dipilih. Hasil docking dibandingkan dengan hasil dari ligan referensi masing-masing.
Hasil: Farmakologi jaringan memprioritaskan AKR1B1 untuk asam klorogenat dan ADORA2B untuk kafein. Pengayaan fungsional mengidentifikasi hubungan yang signifikan dengan sinyal insulin, sinyal glukagon, metabolisme karbohidrat, dan jalur peradangan. Asam klorogenat menghasilkan skor docking sebesar −8,74 kcal/mol terhadap AKR1B1, dibandingkan dengan −10,10 kcal/mol untuk lidorestat, dan membentuk interaksi yang menguntungkan dengan residu situs ikatan. Kafein menghasilkan skor docking yang kurang menguntungkan terhadap ADORA2B (−4,82 kcal/mol) dibandingkan dengan BAY-60-6583 (−7,08 kcal/mol), dengan interaksi kritis yang lebih sedikit.
Kesimpulan: Asam klorogenat dan kafein menunjukkan skor docking yang kurang menguntungkan dibandingkan dengan ligan referensi masing-masing. Temuan ini mengidentifikasi interaksi potensial dengan protein yang relevan dengan T2DM, namun tidak membuktikan aktivitas biologis atau kemanjuran terapeutik. Validasi eksperimental diperlukan untuk mengonfirmasi keterikatan pada target dan efek fungsional. Studi ini mendukung pendekatan komputasional untuk memprioritaskan senyawa alami dan menghasilkan hipotesis mekanistik dalam penemuan obat antidiabetes.

Kata kunci*: asam klorogena, coffea canephora, diabetes melitus tipe 2, kafein, network pharmacology, penambatan molekuler*

INTRODUCTION

Insulin resistance and progressive β-cell dysfunction are the hallmarks of type 2 diabetes mellitus (T2DM), one of the most common chronic metabolic disorders worldwide. T2DM causes persistent hyperglycemia and long-term complications affecting the cardiovascular, renal, neurological, and visual systems. The global prevalence of diabetes continues to rise, with approximately 536.6 million adults currently living with the disease and projections indicating an increase to 783.2 million cases by 2045. Approximately 90% of these cases are classified as T2DM, making it a major global public health challenge.[1] Indonesia is among the countries experiencing a substantial increase in diabetes prevalence, which is estimated to rise from 9.19% in 2020 to 16.09% by 2045.[2] This alarming trend highlights the urgent need for more effective, safer, and sustainable therapeutic strategies.

Conventional antidiabetic agents, including metformin, sulfonylureas, and thiazolidinediones, are widely used to achieve glycemic control in T2DM, although their clinical use is associated with distinct adverse-effect profiles. Metformin commonly causes gastrointestinal disturbances, such as nausea, diarrhea, and abdominal discomfort, whereas sulfonylureas increase the risk of hypoglycemia and weight gain. Thiazolidinediones may cause fluid retention and peripheral edema and can exacerbate heart failure, requiring careful consideration when selecting treatment for patients with pre-existing cardiac conditions.[3] These limitations have encouraged increasing interest in bioactive compounds derived from natural products as potential alternatives or complementary therapies. Among these, *Coffea canephora* (robusta coffee) has

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attracted considerable attention because its green beans contain higher concentrations of chlorogenic acid and caffeine than *Coffea arabica*.[4] Caffeine has been reported to enhance glucose uptake and insulin sensitivity by activating the AMP-activated protein kinase (AMPK) signaling pathway, whereas chlorogenic acid, the primary polyphenolic component of coffee, demonstrates antioxidant, anti-inflammatory, and glucose-regulating properties.[6,7] However, a comprehensive, systems-level understanding of the molecular mechanisms underlying these potential anti-diabetic effects is still lacking.

New developments in computational pharmacology have revolutionized the early stages of drug discovery by offering environmentally sustainable, cost-effective, and rapid methods for identifying therapeutic candidates. Systematic investigation of interactions among bioactive molecules, a specific protein targets, and pathological pathways is facilitated by network pharmacology, which offers mechanistic insights at the systems level. Molecular docking complements this approach by predicting ligand–protein binding modes, binding affinities, and key molecular interactions that may underlie biological activity.[8,9] The utility of these computational approaches has been demonstrated across diverse therapeutic areas, including the identification of potential inhibitors of *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH), highlighting their effectiveness in accelerating early-stage drug discovery and prioritizing promising lead compounds.[10] Compared with conventional experimental screening, these computational methods substantially reduce laboratory costs, experimental time, and chemical waste while facilitating the identification of potential therapeutic targets.[11,12]

Previous studies have reported the interaction of chlorogenic acid and caffeine with individual diabetes-related proteins, including α-glucosidase and PPAR-γ.[13,14] However, these studies primarily focused on single-target analyses and did not comprehensively investigate the molecular mechanisms of these compounds at the systems level. Chlorogenic acid and caffeine have been shown to have anti-diabetic properties in earlier research, however there are still few integrated computational studies that combine network pharmacology and molecular docking to find therapeutic targets and clarify the molecular underpinnings of their anti-diabetic action.

Therefore, the objective of this investigation was to elucidate the molecular mechanisms and identify the therapeutic targets of chlorogenic acid and caffeine from Coffea canephora through the use of an integrated computational approach that integrates molecular docking and network pharmacology.

METHODS

Study design

This *in silico* study investigated the potential antidiabetic activity of chlorogenic acid and caffeine from *Coffea canephora*. An integrated computational workflow combining drug-likeness evaluation, network pharmacology, and molecular docking was applied to identify potential therapeutic targets and characterize ligand–protein interactions associated with Type 2 Diabetes Mellitus (T2DM). The study was conducted from November 1, 2025, to March 29, 2026, and included data collection, computational analysis, and interpretation of the results.

Data source and sampling procedure

Protein targets of chlorogenic acid and caffeine were identified using two databases: SwissTargetPrediction (STP) and STITCH. Canonical SMILES of chlorogenic acid and caffeine were retrieved from the PubChem database on November 3, 2025. The SMILES was submitted to STP with *Homo sapiens* selected as the target species. All predicted targets were retained without applying a probability cutoff. In parallel, protein targets were retrieved from STITCH using the compound query approach in Cytoscape, with a confidence score threshold of 0.04. For each compound, the target lists obtained from

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STP and STITCH were intersected, and only overlapping targets identified by both databases were retained for subsequent analysis. T2DM-associated genes were obtained from the GeneCards and DisGeNET databases on November 15, 2025 using the keyword “Type 2 Diabetes Mellitus”. All genes returned by GeneCards were included without applying a relevance-score cutoff. Only *Homo sapiens* entries were retained, and duplicate genes were removed before further analysis. The overlapping compound-associated targets were intersected with the T2DM-associated gene set to identify potential therapeutic targets.

Variables of the study

The primary compounds analyzed were chlorogenic acid and caffeine derived from *Coffea canephora*. The analyzed targets and computational outcomes included predicted therapeutic targets, protein–protein interaction network characteristics, enriched biological pathways, molecular docking scores, and ligand–protein interaction profiles.

Data collection and computational analysis

Drug-likeness properties of caffeine and chlorogenic acid were predicted using the SwissADME web server (https://www.swissadme.ch/).[14–16] The analysis assessed parameters based on Lipinski’s, Ghose, Veber, Egan, and Muegge to assess the drug-likeness of both compounds.

The canonical SMILES of each compound were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Protein targets associated with each compound were predicted using SwissTargetPrediction (https://www.swisstarget prediction.ch/) under Homo sapiens mode, and the results were imported into Cytoscape 3.9.1 for visualization.[17]

Targets related to T2DM were obtained from GeneCards (https://www.genecards. org/) and DisGeNET (https://www.disgenet.org/search) using the keyword “Type 2 Diabetes Mellitus”.[18] Only Homo sapiens targets were selected. Duplicate entries were removed and overlapping targets between compounds and disease were visualized using the Venny 2.1 web tool (https://bioinfogp.cnb.csic.es/tools/venny/).

The compound–target–disease network was constructed using Cytoscape 3.9.1. Targets shared between the predicted compound targets and T2DM-associated genes were submitted to STRING (https://string-db.org/) to construct a protein–protein interaction (PPI) network.[19] Network topology was analyzed using the cytoHubba plugin in Cytoscape, and candidate hub proteins were ranked according to degree, betweenness, and closeness centrality.[20]

Functional annotation and enrichment analyses of selected targets were performed using the DAVID Bioinformatics Resource (https://david.ncifcrf.gov).[21] The analysis was limited to Homo sapiens with a significance threshold of $p < 0.01$. The results included KEGG pathways and Gene Ontology (GO) terms categorized as Biological Process (BP), Molecular Function (MF), and Cellular Component (CC).

Target proteins selected from the network analysis , were downloaded from the RCSB Protein Data Bank (https://www.rcsb.org/). Protein structures were prepared using UCSF Chimera 1.13 by removing water molecules and native ligands, adding hydrogens, and assigning Gasteiger charges. Ligands were optimized via Gaussian software using Density Functional Theory (DFT) with B3LYP/6-31G basis set. Molecular docking was performed using AutoDock Vina 1.2, following receptor and ligand preparation with AutoDockTools 1.5.7. Docking protocol validation was conducted by redocking the native ligands.[22,23] Docking simulations were performed using the Lamarckian Genetic Algorithm (LGA) with 100 independent runs, while all other parameters were maintained

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at their default values. The best docking poses (lowest binding energy) were visualized using Discovery Studio 2025.

Measurement and Instruments

The computational analyses were performed using a laptop equipped with an AMD Ryzen 3 7320U processor, 8 GB RAM, and a 64-bit operating system. The software used included AutoDock vina 1.2, AutoDock Tools 1.5.7, Discovery Studio Client 2025, UCSF Chimera 1.13, Cytoscape 3.9.1, SwissADME, SwissTargetPrediction, STRING, DAVID Bioinformatics Resource, Gaussian 09W, GaussView 5.0, and Notepad++.

Ethical considerations

Ethical approval was not required because this study was entirely based on publicly available databases and computational analyses without involving human participants, animals, or identifiable personal data.

Data analysis

Drug-likeness was assessed using Lipinski's, Ghose, Veber, Egan, and Muegge rules. Hub proteins were ranked using degree, betweenness, and closeness centrality. GO and KEGG enrichment results with $p < 0.01$ were considered statistically significant. Molecular docking results were evaluated based on predicted docking scores (kcal/mol), ligand-binding poses, hydrogen bonds, and hydrophobic interactions, with each compound compared with the reference ligand for the same target protein. These docking results represent computational predictions and do not establish biological activity.

RESULT

The results present the identification of therapeutic targets, protein–protein interaction network analysis, functional annotation, and molecular interactions of chlorogenic acid and caffeine through an integrated computational approach involving drug-likeness evaluation, network pharmacology, and molecular docking.

Drug likeness analysis

Lipinski's Rule of Five was used to evaluate the drug-likeness profiles of chlorogenic acid and caffeine. Chlorogenic acid had a molecular weight of 354.31 g/mol, nine hydrogen-bond acceptors, six hydrogen-bond donors, and a log P value of −0.39. Caffeine had a molecular weight of 194.19 g/mol, three hydrogen-bond acceptors, no hydrogen-bond donors, and a log P value of 0.08. As shown in Table 1, caffeine fulfilled the evaluated Lipinski's Rule of Five criteria, whereas chlorogenic acid violated one criterion due to its hydrogen-bond donor count exceeding the recommended limit of five. However, this single violation does not necessarily preclude chlorogenic acid from being a potential bioactive compound, although its drug-likeness profile should be interpreted cautiously.

Table 1. Drug Likeness Profile Of Chlorogenic Acid And Caffeine

Compound	Molecular Weight (g/mol)	H-bond Acceptors	H-bond Donors	Log P	Lipinski	GI	BBB	P-gly	Solubility
Chlorogenic acid	354.31	9	6	-0.39	Yes	Low	No	No	Highly soluble in water
Caffeine	194.19	3	0	0.08	Yes	High	No	No	Highly soluble in water

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Target identification and network analysis

Potential therapeutic targets of chlorogenic acid and caffeine were initially predicted using the STITCH and SwissTargetPrediction (STP) databases. For chlorogenic acid, STITCH and STP predicted three and twenty-five targets, respectively, with two overlapping targets identified between the two databases (Figure 1). Similarly, STITCH and STP predicted forty-six and forty-five targets for caffeine, respectively, yielding four common targets. The overlapping targets were considered high-confidence candidates for subsequent analysis because they were consistently identified by both prediction platforms.

To determine their therapeutic relevance to Type 2 Diabetes Mellitus (T2DM), the consensus targets were intersected with T2DM-associated genes retrieved from the GeneCards and DisGeNET databases. All two consensus targets of chlorogenic acid (AKR1B1 and AKR1B10) overlapped with T2DM-related genes. In contrast, only three of the four consensus targets of caffeine (ADORA1, ADORA2A, and ADORA2B) were associated with T2DM, whereas CHIA showed no overlap with the disease-associated gene set and was therefore excluded from further analysis (Figure 1).

The identified targets demonstrated distinct molecular target profiles for chlorogenic acid and caffeine. Chlorogenic acid was mainly associated with the aldo-keto reductase family, whereas caffeine predominantly targeted adenosine receptor family members. These target proteins are known to participate in biological processes related to glucose metabolism, insulin signaling, and inflammatory regulation. Accordingly, the identified targets were subjected to protein–protein interaction (PPI), functional enrichment, and molecular docking analyses.

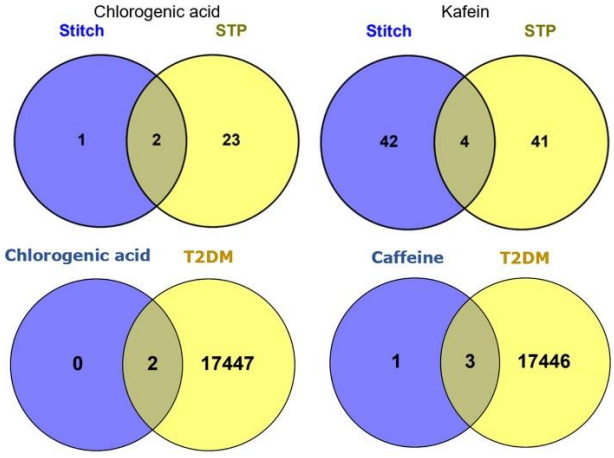


Figure 1. Identification of Consensus Therapeutic Targets of Chlorogenic Acid And Caffeine for Type 2 Diabetes Mellitus.

Protein–Protein Interaction (PPI) and network construction

The biological relationships among the identified T2DM-associated targets were investigated by constructing a protein–protein interaction (PPI) network using the STRING database. The network that resulted was composed of 1,426 edges and 199 nodes, suggesting that there were significant interactions among proteins that were involved in inflammatory responses, insulin signaling, glucose metabolism, and oxidative stress (Figure 2). The high level of network connectivity suggests that these proteins function within closely interconnected biological pathways rather than as isolated molecular targets.

Topological analysis of the PPI network was subsequently performed using the CytoHubba plugin in Cytoscape based on degree, closeness, and betweenness

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centrality. AKR1B1 consistently ranked as the highest-scoring hub protein for chlorogenic acid across all three topological parameters, followed by AKR1B10, SORD, and G6PD (Figure 3). In contrast, ADORA2B was identified as the principal hub protein associated with caffeine, followed by ADORA2A and GNAS. The central positions of AKR1B1 and ADORA2B within the interaction network indicate their potential roles as key regulators of diabetes-related signaling pathways. Based on their high topological significance, AKR1B1 and ADORA2B were selected as representative targets for subsequent molecular docking.

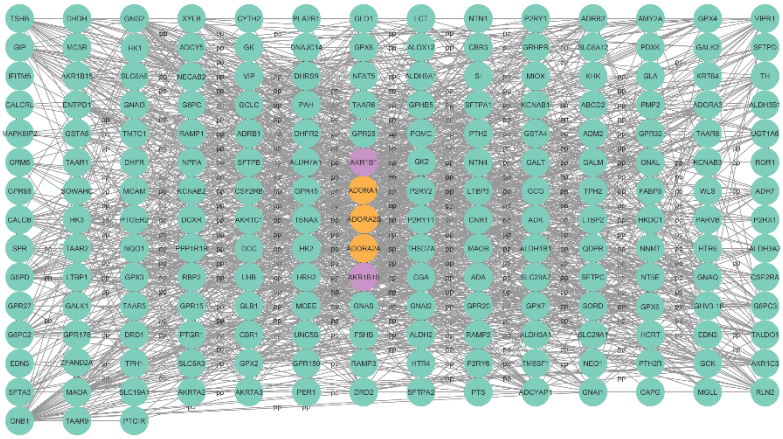


Figure 2. Protein–Protein Interaction (PPI) Network of The Identified Therapeutic Targets Associated with Type 2 Diabetes Mellitus.

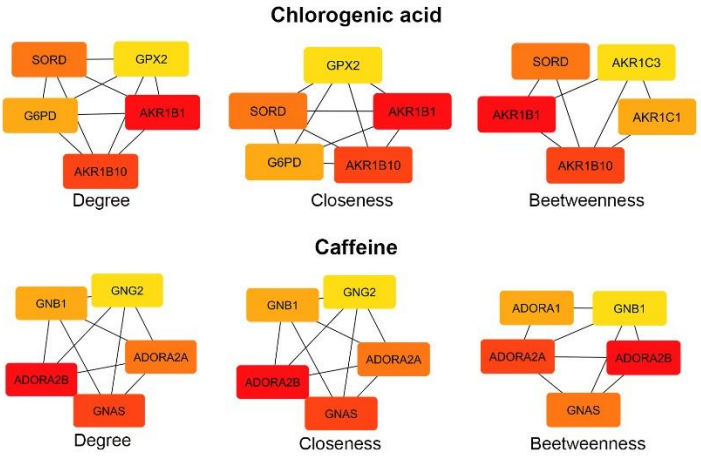


Figure 3. Identification of hub proteins associated with chlorogenic acid and caffeine based on topological analysis of the protein–protein interaction network.

Functional annotation

The identified targets were primarily involved in biological processes related to adenylate cyclase-activating G protein-coupled receptor signaling, lipid metabolism, carbohydrate metabolism and inflammatory responses, as revealed by the Gene Ontology (GO) enrichment analysis (Figure 4). Cellular component analysis showed that most proteins were localized in the plasma membrane, cytosol, and cytoplasm, whereas molecular function enrichment was mainly associated with ATP binding, oxidoreductase activity, and protein kinase activity. These findings indicate that the identified targets participate in multiple biological processes involved in glucose homeostasis, cellular signaling, and metabolic regulation.

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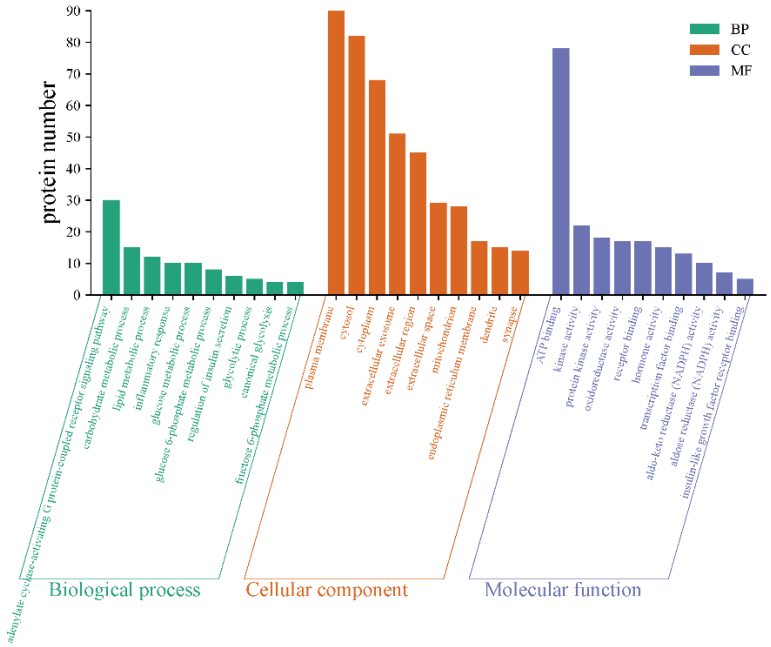


Figure 4. Gene Ontology (GO) Enrichment Analysis of The Identified Therapeutic Targets Associated with Type 2 Diabetes Mellitus.

KEGG pathway enrichment analysis revealed significant enrichment of the identified targets in multiple biological pathways (Figure 5). Among the most enriched pathways were metabolic pathways, insulin signaling, glucagon signaling, galactose metabolism, and Type 2 Diabetes Mellitus (T2DM)-related pathways. The enrichment of these pathways suggests that chlorogenic acid and caffeine may exert anti-diabetic effects by modulating multiple interconnected metabolic and signaling pathways rather than acting through a single molecular target.

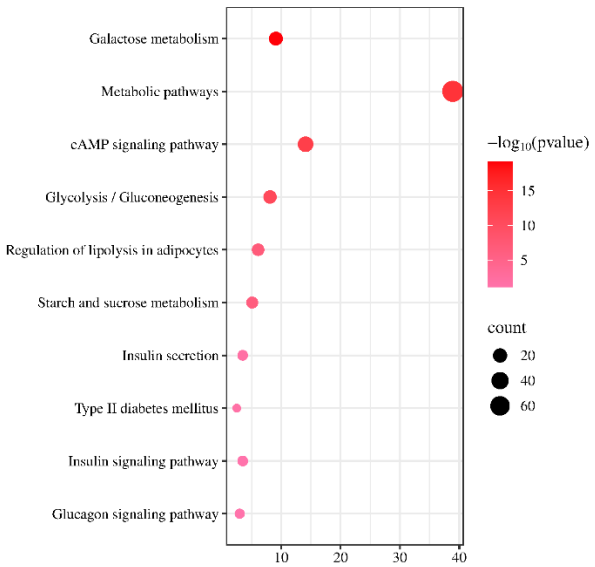


Figure 5. KEGG Pathway Enrichment Analysis of The Identified Therapeutic Targets Associated with Type 2 Diabetes Mellitus.

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Molecular docking

The docking scores of chlorogenic acid and caffeine against their respective target proteins are presented in Table 2. Chlorogenic acid had a docking score of −8.74 kcal/mol against AKR1B1 (PDB ID: 1Z3N), whereas the native ligand, lidorestat, scored −10.10 kcal/mol under the same docking protocol. The chlorogenic acid score was therefore 1.36 kcal/mol less negative than that of lidorestat. For ADORA2B (PDB ID: 7XY6), caffeine had a docking score of −4.82 kcal/mol, compared with −7.08 kcal/mol for the native ligand, BAY 60-6583, corresponding to a difference of 2.26 kcal/mol. Both compounds thus had less negative docking scores than their respective native ligands. These comparisons were restricted to ligands docked against the same protein, because scores obtained from different target proteins do not provide a reliable basis for directly ranking the compounds. Furthermore, docking scores are computational estimates and do not establish experimentally measured binding affinities, equivalent activity, or antidiabetic efficacy.

The predicted ligand–protein interaction profiles are illustrated in Figure 6. Chlorogenic acid was positioned within the AKR1B1 binding pocket, where the interaction analysis identified two conventional hydrogen bonds with Tyr48 and Thr113. Hydrophobic contacts were described separately and included π–alkyl interactions with Trp20 and Leu300 and an alkyl interaction with Cys298. In addition, a π–sulfur contact was identified with Cys303 and classified separately from the hydrogen bonds and hydrophobic contacts (Figure 6A). Together, these contacts describe the predicted interaction pattern surrounding chlorogenic acid within the binding pocket. The chlorogenic acid pose also showed qualitative overlap with the native ligand pose, suggesting that the two ligands occupied a similar region of the AKR1B1 pocket. The interaction profile of lidorestat is presented in Figure 6C to facilitate comparison of their predicted contact patterns. Although these observations provide a structural hypothesis for chlorogenic acid binding to AKR1B1, the presence of multiple contacts and qualitative pose overlap does not establish binding stability or enzyme inhibition, which require further validation.

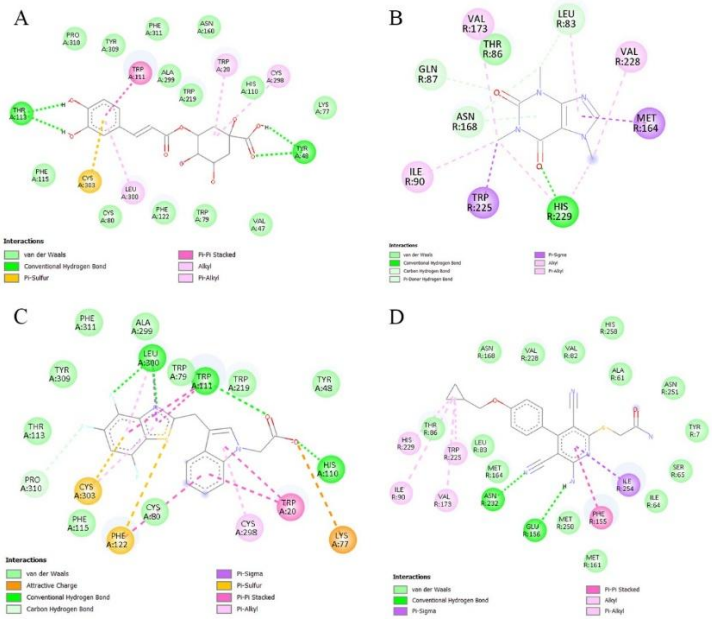


Figure 6. Molecular docking interaction profiles of chlorogenic acid and caffeine with AKR1B1 and ADORA2B compared with their respective native ligands. (A) Chlorogenic

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acid–AKR1B1, (B) caffeine–ADORA2B, (C) Lidorestat–AKR1B1, and (D) BAY 60-6583–ADORA2B interaction profiles.

Caffeine exhibited a distinct binding mode within ADORA2B (Figure 6B). The ligand was positioned near the extracellular binding cavity rather than occupying the central ligand-binding pocket. Caffeine formed four conventional hydrogen bonds with His229, Gln87, Leu83, and Asn168, together with hydrophobic interactions involving Met164, Trp225, His229, Leu83, and Val228. Although multiple hydrogen bonds were observed, these interactions were distributed across the peripheral region of the receptor, resulting in fewer contacts within the core binding pocket than those observed for the native ligand. Consequently, caffeine displayed a less compact binding orientation and reduced overlap with the native ligand-binding site. The interaction pattern of the native ligand (BAY 60-6583) bound to ADORA2B is shown in Figure 6D to facilitate comparison with the docking pose of caffeine.

Table 2. Molecular Docking Scores Of Chlorogenic Acid And Caffeine Against Their Respective Target Proteins.

Compound	Target Protein (PDB ID)	Native Ligand	Docking Score (kcal/mol)	Native Ligand Score (kcal/mol)
Chlorogenic acid	AKR1B1 (1Z3N)	Lidorestat	−8.74	−10.10
Caffeine	ADORA2B (7XY6)	BAY 60-6583	−4.82	−7.08

Overall, the docking results should be interpreted separately for each protein target. For AKR1B1, chlorogenic acid exhibited a less negative predicted docking score than lidorestat, although its predicted pose showed qualitative overlap with the native ligand-binding region. For ADORA2B, caffeine also exhibited a less negative predicted docking score than BAY 60-6583 and showed reduced overlap with the native ligand-binding site. These findings provide target-specific structural hypotheses for the interactions of chlorogenic acid with AKR1B1 and caffeine with ADORA2B. However, the predicted docking scores and interaction profiles alone are insufficient to establish binding affinity, target modulation, or antidiabetic efficacy. Further experimental validation is required to determine the biological relevance of these predicted interactions.

DISCUSSION

The present study employed an integrated computational strategy combining drug-likeness evaluation, network pharmacology and molecular docking to investigate the anti-diabetic potential of chlorogenic acid and caffeine from *Coffea canephora*. Drug-likeness analysis showed that caffeine fulfilled the evaluated Lipinski's Rule of Five criteria, whereas chlorogenic acid exhibited one violation due to its hydrogen-bond donor count exceeding the recommended limit. This single violation does not necessarily preclude chlorogenic acid from being a potential bioactive compound, but its drug-likeness profile should be interpreted cautiously. Previous studies have reported pharmacokinetic characteristics and biological activities of these compounds that warrant further investigation.[25,26] However, their oral bioavailability and suitability for drug development cannot be established from Lipinski's Rule of Five alone.

Network pharmacology analysis revealed distinct molecular targets for the two bioactive compounds. Chlorogenic acid primarily targeted AKR1B1 and AKR1B10, whereas caffeine was mainly associated with ADORA1, ADORA2A, and ADORA2B. The subsequent PPI analysis identified AKR1B1 and ADORA2B as the highest-ranked hub proteins based on the network analysis criteria, suggesting that these proteins occupy central positions within the diabetes-related interaction network. AKR1B1 is a key enzyme in the polyol pathway, catalyzing the conversion of glucose into sorbitol under hyperglycemic conditions.[27] Excessive activation of this pathway promotes oxidative

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stress, inflammation, and diabetic microvascular complications, making AKR1B1 a potential target of interest in T2DM.[28] Conversely, ADORA2B has been reported to regulate insulin sensitivity, glucose utilization, inflammatory signaling, and macrophage polarization through adenosine-mediated pathways.[29,30] The identification of AKR1B1 and ADORA2B as hub proteins highlights their central positions within the analyzed diabetes-related interaction network and provides a basis for investigating their potential associations with chlorogenic acid and caffeine, respectively. These network-based associations prioritize candidate targets for further investigation but do not establish direct compound–target interactions or confirm antidiabetic effects.

GO and KEGG analyses further supported these findings by demonstrating that the identified targets were primarily associated with metabolic pathways, insulin signaling, glucagon signaling, carbohydrate metabolism, and inflammatory processes. The results of this study are consistent with previous network pharmacology studies, which have demonstrated that natural products often demonstrate therapeutic effects through multi-target and multi-pathway mechanisms rather than operating on a single molecular target.[31,32] The enrichment of oxidoreductase activity is particularly relevant because oxidative stress is recognized as one of the major contributors to pancreatic β-cell dysfunction and insulin resistance in T2DM. Similarly, ATP-binding proteins and protein kinases identified in this study participate in intracellular signaling pathways regulating glucose homeostasis, further supporting the systems-level mechanism predicted by the network analysis.

Molecular docking analysis showed that chlorogenic acid had a docking score of −8.74 kcal/mol against AKR1B1, compared with −10.10 kcal/mol for the native inhibitor, lidorestat, on the same target. Although chlorogenic acid had a less negative docking score than lidorestat, its predicted pose occupied a similar region of the AKR1B1 binding pocket. Previous studies investigating chlorogenic acid interactions with diabetes-related enzymes provide context for further examination of this predicted binding mode.[33] The interaction analysis identified conventional hydrogen bonds with Tyr48 and Thr113, hydrophobic contacts involving Trp20, Cys298, and Leu300, and a separate π–sulfur contact with Cys303. Tyr48 has been implicated in ligand recognition by AKR1B1 inhibitors, while Trp111 and Leu300 have been discussed in relation to inhibitor binding within the specificity pocket.[34] The literature-described role of Trp111 should be distinguished from the Trp20 contact reported in the present docking analysis. The qualitative overlap between the chlorogenic acid and lidorestat poses supports a hypothesis of binding within a similar pocket region, but does not establish equivalent affinity, binding stability, or inhibitory activity.

Although chlorogenic acid did not directly interact with all key binding residues, it exhibited a favorable binding orientation supported by multiple hydrogen-bonding and hydrophobic interactions. Similar interaction patterns have been reported for several natural polyphenols, where inhibitory activity is governed by the overall binding conformation and interaction network rather than direct interactions with every conserved residue.[35,36] These structural observations provide a hypothesis for chlorogenic acid binding within the AKR1B1 pocket. However, the predicted interactions alone are insufficient to establish that chlorogenic acid inhibits AKR1B1. Enzyme inhibition assays are required to determine whether the predicted binding mode translates into measurable inhibitory activity.

Caffeine exhibited a less negative predicted docking score against ADORA2B (−4.82 kcal/mol) than the native ligand BAY 60-6583 (−7.08 kcal/mol). Although caffeine formed several hydrogen bonds and hydrophobic interactions, the ligand adopted a more peripheral binding orientation and showed limited overlap with the native ligand-binding

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pocket. Previous structural studies have demonstrated that high-affinity ADORA2B ligands generally interact with conserved residues including Thr89, Phe173, Asn254, Ser279, and His280, which play essential roles in receptor activation and ligand stabilization.[37] The absence of predicted contacts with these residues may reflect the distinct binding orientation of caffeine relative to the native ligand. However, this difference in predicted interactions does not by itself establish reduced receptor affinity or determine whether caffeine activates or inhibits ADORA2B. Previous studies have suggested that caffeine can influence glucose metabolism through mechanisms involving adenosine receptor signaling and other cellular pathways, including AMPK-related signaling.[38,39] These previously reported mechanisms provide broader biological context but do not establish that caffeine modulates ADORA2B through the binding mode predicted in the present study.

Collectively, the integration of network pharmacology and molecular docking provides complementary computational evidence for prioritizing candidate compound–target associations related to T2DM. The findings support further investigation of the predicted chlorogenic acid–AKR1B1 interaction and the caffeine–ADORA2B interaction as separate target-specific hypotheses, rather than establishing that one compound is more promising than the other. The integrated computational workflow may serve as an efficient strategy for prioritizing bioactive compounds and candidate targets before experimental screening. Nevertheless, these predictions require experimental validation before conclusions can be drawn regarding target modulation or therapeutic potential in T2DM.

Future studies should focus on validating the predicted inhibitory activity of chlorogenic acid against AKR1B1 through enzyme inhibition assays, followed by in vitro investigations using insulin-resistant or pancreatic β-cell models to evaluate its effects on glucose metabolism and oxidative stress. Subsequent in vivo studies in diabetic animal models will be essential to assess its pharmacological efficacy, safety profile, and pharmacokinetic characteristics before advancing to preclinical development. Nevertheless, these findings are derived from computational analyses and should be interpreted with caution. Experimental validation is essential to determine whether the predicted compound–target interactions translate into measurable biological effects and whether these effects are relevant to T2DM.

CONCLUSION

This study integrated network pharmacology and molecular docking to prioritize putative T2DM-associated targets and explore predicted interactions of chlorogenic acid and caffeine from *Coffea canephora*. Network analysis prioritized AKR1B1 and ADORA2B as hub proteins associated with chlorogenic acid and caffeine, respectively, while functional enrichment identified associations with pathways related to glucose metabolism and insulin signaling. Molecular docking showed that chlorogenic acid had a predicted docking score of −8.74 kcal/mol against AKR1B1, compared with −10.10 kcal/mol for lidorestat, whereas caffeine scored −4.82 kcal/mol against ADORA2B, compared with −7.08 kcal/mol for BAY 60-6583. Thus, both compounds had less negative predicted docking scores than their respective native ligands. These findings provide target-specific structural hypotheses for chlorogenic acid–AKR1B1 and caffeine–ADORA2B interactions but do not establish binding affinity experimentally, target modulation, or antidiabetic efficacy. Further *in vitro* and *in vivo* studies are required to validate these predicted interactions and evaluate the biological activity and therapeutic potential of both compounds.

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