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Article

Computational prediction of chlorogenic acid binding to disease-linked proteins CHIT1 and CHI3L1

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SUMMARY

Chlorogenic acid is a common dietary plant compound with health benefits for diseases such as asthma and fibrosis. Interestingly, the diseases in which chlorogenic acid shows benefits are also linked to high activity of the chitinase chitotriosidase-1 (CHIT1) and the signaling protein chitinase-3-like protein-1 (CHI3L1), which binds to but cannot digest chitin. Given these associations, we hypothesized that chlorogenic acid binds strongly to CHIT1 and CHI3L1, which may inhibit their functions. To test this hypothesis, we used molecular docking, a computational method that predicts how molecules interact. Compared to known chitinase inhibitors and several other natural compounds, chlorogenic acid was predicted to bind strongly and specifically to both CHIT1 and CHI3L1. Importantly, the docking showed that chlorogenic acid binds to both CHIT1 and CHI3L1 at their chitin-binding regions, which are critical for their biological functions, similarly to the known inhibitors of these two proteins. Our results suggest a novel molecular mechanism for chlorogenic acid, going beyond the antioxidant activity that is well-known to underlie its benefits in diseases. Our study provides a testable foundation for future experiments to validate these interactions and explore whether targeting these proteins could lead to new therapeutic strategies for a range of chronic diseases.

INTRODUCTION

Chitin is a highly abundant, natural polymer of N-acetylglucosamine, providing important support for arthropod exoskeletons, fungal cell walls, and nematode eggs (1). To break down this tough material, enzymes called chitinases are produced by many organisms, such as bacteria, plants, and animals (1). Humans produce not only active chitinases such as chitotriosidase-1 (CHIT1), but also chitinase-like proteins such as chitinase-3-like protein 1 (CHI3L1) that bind to chitin but cannot digest it (2, 3). In humans, these chitinase-like proteins are important because they regulate inflammation, and their abnormal expression is linked to many diseases (2, 3). Either binding to chitin or mutational disruption of the chitin-binding domain prevents chitinase-like proteins from interacting with their normal partners, thereby hindering their functions (4-6). Chitinases and CHI3L1 are increasingly recognized as key players in various diseases. High levels of CHIT1 are correlated not only with fibrosis but also inflammation (3, 7). Abnormally high CHI3L1 expression levels are linked to 18 types of tumors and 26 types of other non-cancerous diseases, and in some cancers and tumors this elevated CHI3L1 actively facilitates cancer development in different ways (2). High levels of CHI3L1 lead to degenerative outcomes in many inflammatory and immunological diseases such as pulmonary fibrosis, alcoholic liver fibrosis, multiple sclerosis, and Alzheimer's disease (2, 8, 9). As a result, CHIT1 and CHI3L1 are increasingly recognized as promising targets for new medicines. Thus, a compound that could safely block CHIT1 and CHI3L1 activity might offer a new way to treat inflammatory and immunological disease conditions.

Potential sources for a new therapeutic compound include the plant-derived molecule chlorogenic acid. Chlorogenic acid is a common plant metabolite found in tea and coffee, as well as some fruits such as berry fruits and apples (10). Chlorogenic acid is famous for its many reported health benefits, such as anti-oxidation, anti-inflammation, cardiovascular protective effects, and neuroprotection (11). Studies have shown that chlorogenic acid is beneficial for treating many diseases, especially those that are chronic and related to aging (11). It is important to note that many diseases associated with therapeutic benefit to chlorogenic acid express abnormally high levels of CHIT1 and CHI3L1 protein, including asthma, pulmonary fibrosis, neurological disorders, and cancer (2, 3, 7). Scientists have usually explained the therapeutic effects by pointing to chlorogenic acid's strong antioxidant activity and its general ability to reduce inflammation (10, 11). However, the close match between the diseases ameliorated by chlorogenic acid and the diseases driven by CHIT1 and CHI3L1 suggests a more direct link might be possible.

Therefore, we hypothesized that chlorogenic acid binds strongly to CHIT1 and CHI3L1, which could lead to interference of their functions. Specifically, we wondered whether chlorogenic acid could act as a direct inhibitor by binding the active site of CHIT1. To test this hypothesis, we used a computer method called molecular docking. This technique predicts how a small molecule fits into the three-dimensional structure of a protein and calculates how tightly it binds (12). In this study, our results showed that chlorogenic acid binds CHIT1 and CHI3L1 with high predicted affinity comparable to known inhibitors, and that this binding is specific rather than general across proteins. Docking further indicated that chlorogenic acid engages functional sites on both proteins, suggesting potential inhibitory activity. These findings identified chlorogenic acid as a promising small molecule candidate for modulating chitinase-related pathways, with possible relevance to diseases in which these proteins play a role.

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RESULTS

In silico molecular docking has been a powerful tool in drug discovery for decades. First developed in the early 1980s with programs like DOCK, this method allows researchers to predict ligand binding by calculating complementary shapes and chemical features between the molecule and protein (13). Today, docking is widely used to screen compound libraries, identify potential binding sites, and guide experimental research (14). We performed molecular docking to assess the binding of chlorogenic acid to CHI3L1 that has the Protein Data Bank (PDB) ID of 1NWR and CHIT1 (PDB ID: 1LQ0). While both CHIT1 and CHI3L1 have known chitin-binding domains, compounds binding to other sites of the protein might also affect the proteins' functions, such as by blocking the interface of protein-protein interaction. Therefore, our docking analyses were initially performed as blind docking, meaning that the entire protein surface was searched without specifying a

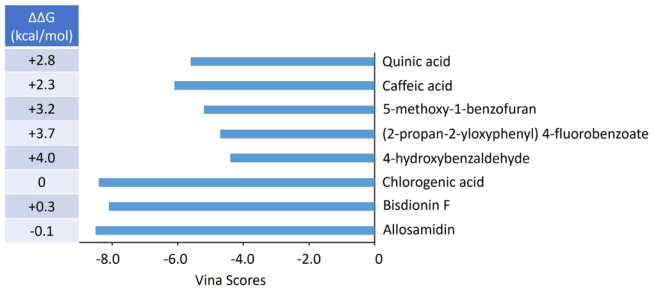

Figure 1: Molecular docking predicted strong binding of chlorogenic acid to chitotriosidase-1 (CHIT1). The bar graph shows Vina scores for the compounds studied. A more negative score indicates stronger and more favorable binding. Allosamidin and bisdionin F are known inhibitors of chitinases and serve as positive controls. The predicted binding free energy difference (ΔΔG) shown on the left are values compared to that of chlorogenic acid.

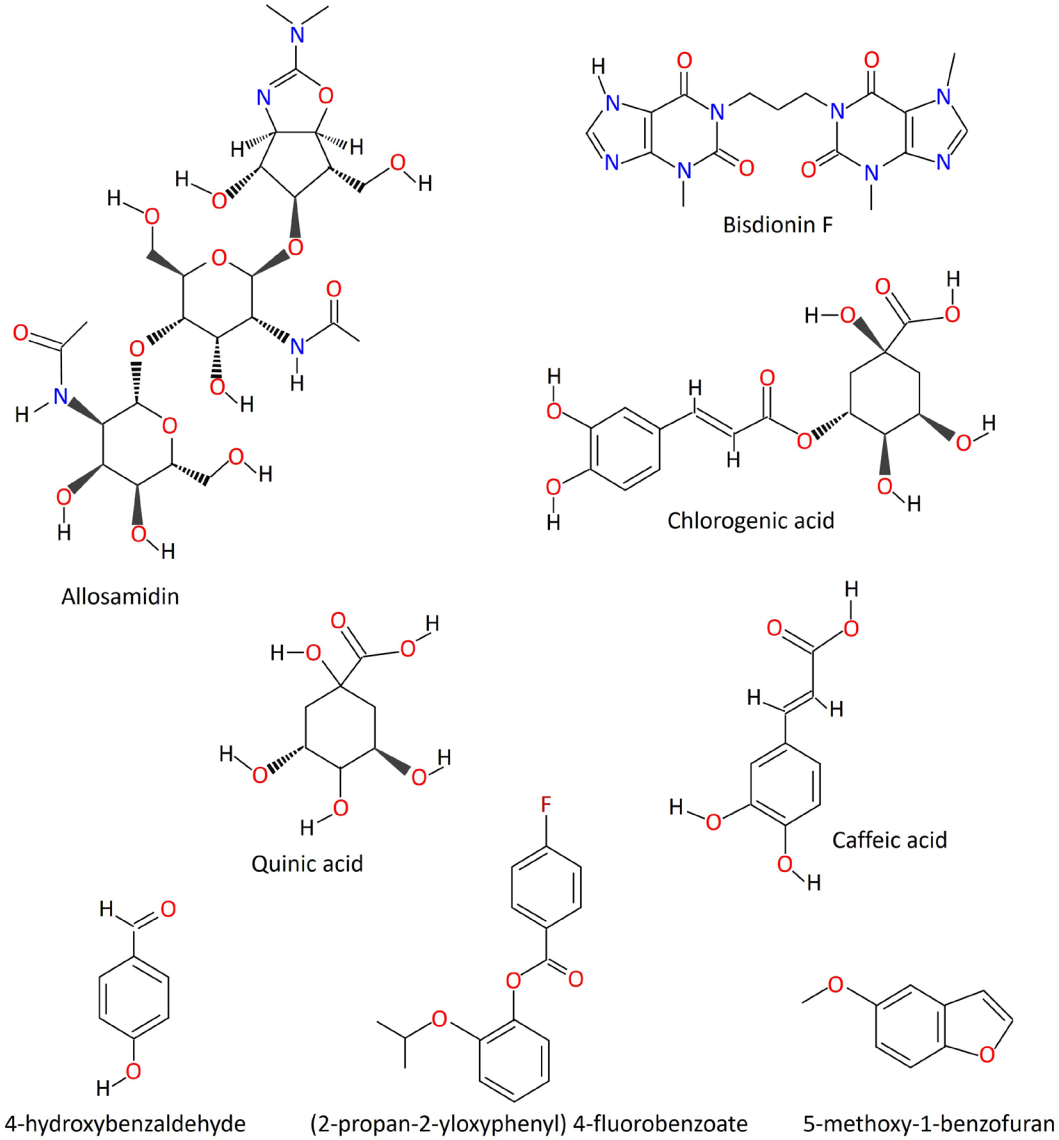

Figure 2: Chemical structures of chlorogenic acid and the other compounds studied. Chemical structures of the compounds studied with all chemical bonds shown in black. Each compound is labeled with its name below its chemical structure.

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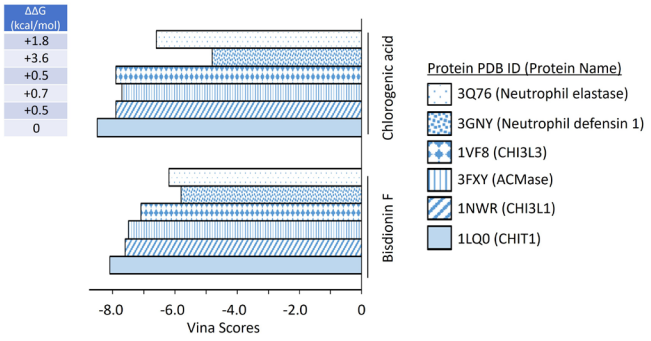

Figure 3: Chlorogenic acid showed binding specificity to CHIT1 and chitinase-3-like protein-1 (CHI3L1). The bar graph shows Vina scores for docking of chlorogenic acid or bisdionin F to the six proteins studied, indicated by different patterns. A more negative score indicates stronger and more favorable binding. The ΔΔG shown on the left are values compared to that of docking chlorogenic acid to 1LQ0 (CHIT1).

predefined binding site. Molecular docking results are given as Vina scores (12). The Vina score typically appears as a negative number for favorable binding interactions because it approximates the predicted binding free energy (ΔG) between molecules. A more negative score indicates stronger and more favorable binding. However, in cases where interactions are unfavorable (e.g., repulsive electrostatic forces), the score can be positive. Additionally, while the Vina score is useful for ranking binding affinities of different poses or ligands at the same binding site, it should be interpreted as a relative rather than an absolute thermodynamic value. Molecular docking of chlorogenic acid to CHIT1 resulted in a Vina score of -8.4 kcal/mol; in comparison, docking CHIT1 with bisdionin F and allosamidin, two known inhibitors of chitinases, resulted in Vina scores of -8.1 kcal/mol and -8.5 kcal/mol, respectively (**Figure 1**) (15, 16). These results suggested that chlorogenic acid can bind as strongly as the known inhibitors to CHIT1. Chlorogenic acid has one aromatic ring, while bisdionin F has two, and allosamidin has none (**Figure 2**). Aromatic rings can contribute to ligand-protein interactions because they often participate in Pi-stacking or hydrophobic interactions with aromatic residues in the protein. These three compounds also differ in the types and amounts of polar groups, such as -OH and -COOH, which make them hydrophilic. Despite these differences, the three compounds yielded comparable binding scores, suggesting that chlorogenic acid can bind as strongly as the known inhibitors to CHIT1, though potentially via different chemical interactions

We wondered whether CHIT1 would show strong Vina scores when docking any compound. Hence, in addition to chlorogenic acid, we also performed molecular docking of CHIT1 with other compounds, including 4-hydroxybenzaldehyde, (2-propan-2-yloxyphenyl) 4-fluorobenzoate, and 5-methoxy-1-benzofuran (**Figure 2**). These compounds were randomly selected from a published database of natural compounds (17). Molecular docking of these compounds to CHIT1 resulted in Vina scores ranging from -4.4 kcal/mol to -5.2 kcal/mol (**Figure 1**). Based on the relationship ΔΔG = -RT ln(Kd2/Kd1), in which Kd is the equilibrium dissociation constant measuring how tightly a ligand binds to its target, the differences between Vina scores corresponded to approximately 222- to 860-fold stronger binding affinity for chlorogenic acid compared to the control compounds. In addition, we performed molecular docking of CHIT1 with caffeic acid and quinic acid, the two compounds that result from metabolic breakdown of chlorogenic acid (**Figure 2**) (18). The docking yielded Vina scores of -6.1 kcal/mol for caffeic acid and -5.6 kcal/mol for quinic acid (**Figure 1**). Chlorogenic acid is essentially caffeic acid and quinic acid linked by an ester bond (**Figure 2**). The lower binding scores of the two fragments suggested that the full molecule binds more strongly than either fragment alone, likely because it combines the favorable interactions of both parts with CHIT1. We also asked whether chlorogenic acid would show strong Vina scores when docking to any protein. We performed molecular docking of chlorogenic acid to human neutrophil elastase (HNE, PDB ID: 3Q76) and human neutrophil defensin 1 (HNP-1, PDB ID: 3GNY), which were randomly chosen from the PDB database (19). The docking resulted in Vina scores of -6.6 kcal/mol and -4.8 kcal/mol for HNE and HNP-1, respectively (**Figure 3**). These values corresponded to 21- and 439-folds lower binding affinity compared to the -8.4 kcal/mol score when docking chlorogenic acid to CHIT1. In order to further examine the binding specificity of chlorogenic acid to chitinases, we also performed docking with the human acidic mammalian chitinase (AMCase, PDB: 3FXY) and the mouse chitinase-3-like protein 3 (CHI3L3, PDB: 1VF8). Chlorogenic acid was predicted to bind AMCase and CHI3L3 with Vina scores of -7.7 kcal/mol and -7.9 kcal/mol, respectively, whereas the corresponding binding scores for bisdionin F were -7.5 kcal/mol and -7.1 kcal/mol (**Figure 3**). Therefore, chlorogenic acid was consistently predicted to bind to chitinases and chitinase-like proteins with high affinity comparable to bisdionin F. Altogether, the docking results showed that the predicted strong binding affinity of chlorogenic acid to CHIT1 is a specific protein-ligand relation. We next performed molecular docking of the compounds with CHI3L1. Similar to the observations with CHIT1, chlorogenic acid showed strong binding affinity to CHI3L1, as shown by the Vina scores of -7.9 kcal/mol (**Figure 4**). Similarly, bisdionin F and allosamidin showed Vina scores of -7.6 kcal/mol and -7.4 kcal/mol, respectively. In contrast, the other 5 examined

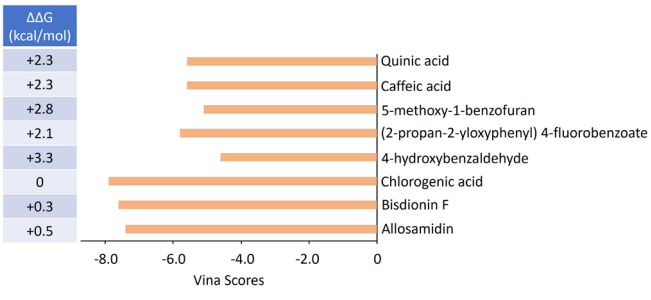

Figure 4: Molecular docking predicted strong binding of chlorogenic acid to CHI3L1. The bar graph shows Vina scores for docking of the compounds to CHI3L1. A more negative score indicates stronger and more favorable binding. Allosamidin and bisdionin F are known inhibitors of chitinases and serve as positive controls. The ΔΔG shown on the left are values compared to that of chlorogenic acid.

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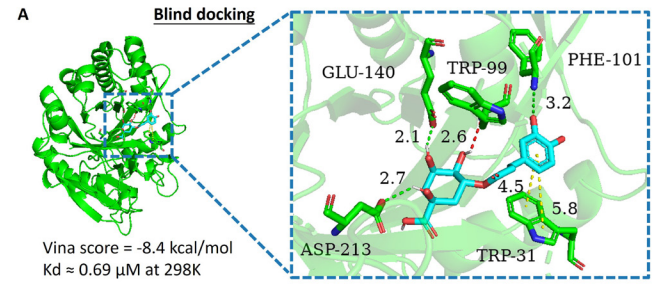

Bond Information			
Symbols	Types	Numbers	Distance
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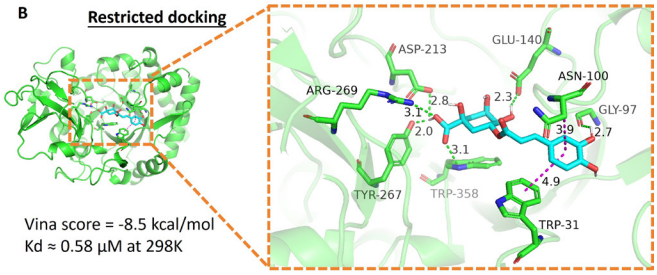
- - -	Pi-Pi Stacked	2	4.5; 5.8
- - -	Unfavorable Donor-Donor	1	2.6



Bond Information			
Symbols	Types	Numbers	Distance
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·····	Pi-Pi Stacked	1	4.9
·····	Pi-Sigma	1	3.9

Figure 5: Chlorogenic acid is predicted to bind the activity center of CHIT1. The chlorogenic acid molecule is shown in light blue, with red bonds indicating the presence of oxygen atoms. The CHIT1 amino acid residues that interact with chlorogenic acid are highlighted in green and labeled. The types of molecular interactions are indicated by dashed lines with different color codes. Panel A and Panel B are blind docking and restricted docking, respectively.

compounds showed Vina scores ranging from -4.6 kcal/mol to -5.8 kcal/mol. These values corresponded to 35- and 264-fold lower binding affinity compared to chlorogenic acid. Therefore, molecular docking predicted a specific protein-ligand relationship between chlorogenic acid and CHI3L1.

To understand how the binding of chlorogenic acid may affect CHIT1, we visualized the blind docking results by using Discovery Studio and Pymol (20, 21), to know the protein residues that interact with chlorogenic acid. Blind docking predicted that chlorogenic acid binds to CHIT1 at the protein's active site, involving the key residues including Glu-140, Asp-213, and Trp-31 (**Figure 5A**) (15). Because blind docking may be less predictive than more restricted experiments, we further performed restricted docking by centering on the active site of CHIT1 with the grid box being around one tenth of the blind docking. The grid box defines the three-dimensional region of the protein where the docking algorithm searches for possible ligand binding configurations. While the blind docking Vina score was -8.4 kcal/mol for chlorogenic acid's binding to CHIT1, the restricted docking Vina score was -8.5 kcal/mol (**Figure 5B**). Compared to blind docking, the restricted docking predicted that the binding of chlorogenic acid to CHIT1 takes a slightly different conformation, involving more amino acid residues known to be important within the active site, including not only Pi-Pi stacked interaction with Trp-31 and conventional hydrogen bonds with Glu-140 and Asp-213, but also Pi-Sigma interaction with Asn-100 and a conventional hydrogen bond with Trp-358 (**Figure 5B**). In addition, chlorogenic acid forms hydrogen bonds with Gly-97, Tyr-267, and Arg-269. The same restricted docking predicted that both bisdionin F and allosamidin also bind to CHIT1's active site, interacting with key residues such as Asp-213 and Trp-358 (**Figure 6**). Compared to chlorogenic acid, both bisdionin F and allosamidin were predicted to form fewer hydrogen bonds but more other types of interactions, including Pi-Pi and Pi-Sigma interactions, resulting in Vina scores similar to chlorogenic acid. In contrast, the much weaker binding of the other compounds to CHIT1 was shown by not only fewer hydrogen bonds but by unfavorable interactions, as exemplified by caffeic acid, quinic acid, and 4-hydroxybenzaldehyde (**Figure 6**). Therefore, chlorogenic acid is predicted to act as a direct inhibitor of CHIT1 by binding directly to the active site.

We next performed restricted docking of chlorogenic acid to CHI3L1. The results showed that chlorogenic acid binds the chitin-binding site of CHI3L1 (22), forming conventional hydrogen bonds and Pi-Pi stacked interactions with key residues including Trp-31, Trp-69, Arg-263, and Trp-352 (**Figure 7**). It has been reported that a chemical inhibitor, K284, binds to the chitin-binding site of CHI3L1, thereby blocking CHI3L1 binding to its receptor IL-13Rα2 and resulting in suppression of CHI3L1 signaling and cancer cell growth (5). Restricted docking also showed that K284 binds to the chitin-binding site of CHI3L1, involving the key residues including Trp-99, Trp-212, Arg-263, and Trp-352 (**Figure 8**). We compared chlorogenic acid with K284. Chlorogenic acid is smaller than K284, and its CHI3L1 binding site largely overlaps with a part of the binding site of K284 (**Figure 8**). While K284 showed a Vina score of -9.0 kcal/mol with CHI3L1, chlorogenic acid showed -8.5 kcal/mol (**Figure 7, 8**). Taken together, these results suggested that chlorogenic acid binding to CHI3L1 may act as an inhibitor, like K284.

DISCUSSION

We tested the hypothesis that chlorogenic acid, a common compound in the human diet with known therapeutic benefits, might work by directly interacting with CHIT1 and CHI3L1 (10, 11). Using molecular docking, we provided computational evidence predicting that chlorogenic acid could bind to both CHIT1 and CHI3L1. More importantly, our analysis predicted that chlorogenic acid binds directly to the catalytic active site of CHIT1 and the chitin-binding domain of CHI3L1. These results strongly suggest that chlorogenic acid may function as both a direct, competitive inhibitor of CHIT1 enzymatic activity and an inhibitor of CHI3L1 signaling function. Therefore, the merging of our computational evidence with the known biological activities of chlorogenic acid presents a novel and mechanistically coherent explanation for its role in human health.

For a long time, scientists have explained the health benefits of chlorogenic acid mostly by its antioxidant activity (11). While protection against oxidative damage is critical, our results suggest a more specific possibility. Based on our findings, scientists may want to experimentally test the hypothesis that chlorogenic acid might also work by directly targeting CHIT1 and CHI3L1 in ameliorating related diseases such as severe asthma and other inflammatory or

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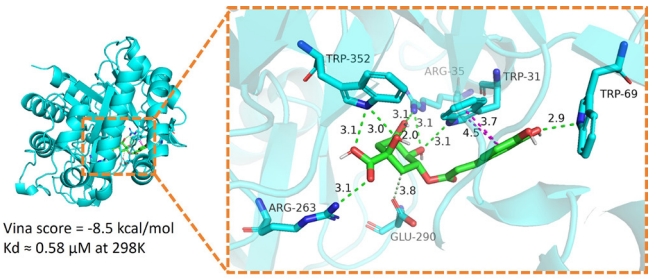
Figure 6: Comparison between chlorogenic acid and the other compounds docking with CHIT1. Restricted docking was performed for CHIT1 (PDB ID: 1LQ0) with the compounds. The types of molecular interactions are indicated by dashed lines with different color codes.

immunological diseases. While a detailed pharmacokinetic analysis is outside the scope of this study, it is worth noting that oral chlorogenic acid has limited bioavailability (18, 23), though alternative routes such as nasal administration can dramatically improve delivery to lung tissues (24). Thus, formulation and delivery methods should be considered in future experimental validation of our computational findings.

CHIT1 is a classic enzyme with a direct functional site. Our model predicts chlorogenic acid binds to CHIT1 in the enzyme active site, which would physically block CHIT1's enzyme function. Future studies should measure the effects of chlorogenic acid on CHIT1 activity. Unlike CHIT1, CHI3L1 functions as a signaling molecule instead of a working enzyme (2), but the chitin-binding domain is important for CHI3L1 to bind its own receptor and consequently activating its signaling function. As chlorogenic acid is predicted to bind to CHI3L1 at the chitin-binding domain, it would also be interesting to see whether site-directed mutagenesis of the key residues can abolish chlorogenic acid's binding to the protein.

Our docking predictions used two independent strategies and showed consistency. First, we performed blind docking without providing any prior information about the binding site. This approach independently placed chlorogenic acid at the catalytic active site of CHIT1. We then performed



Bond Information			
Symbols	Types	Numbers	Distance
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·····	Pi-Pi Stacked	2	3.7; 4.5
·····	Carbon Hydrogen Bond	1	3.8

Figure 7: Chlorogenic acid is predicted to bind CHI3L1 at the chitin-binding domain. Restricted molecular docking was performed for chlorogenic acid with CHI3L1 (PDB ID: 1NWR). The chlorogenic acid molecule is shown in green, with red bonds indicating the presence of oxygen atoms. The CHI3L1 amino acid residues that interact with chlorogenic acid are highlighted in bright blue and labeled. The types of molecular interactions are indicated by dashed lines with different color codes.

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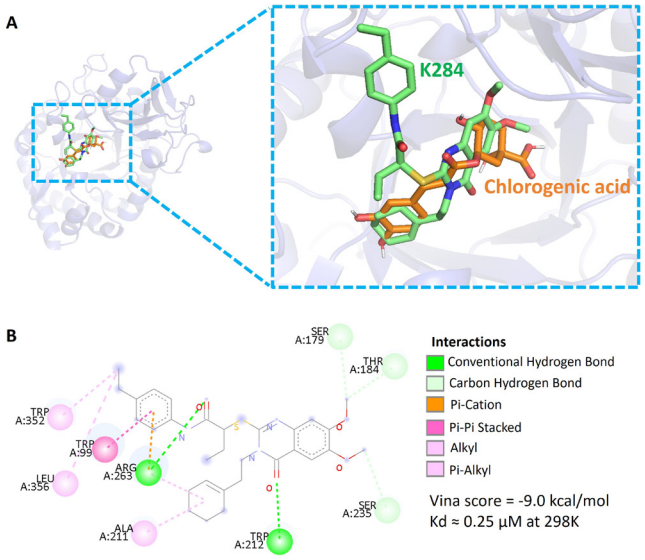

Figure 8: Comparison between chlorogenic acid and K284 in binding CHI3L1. Restricted molecular docking was performed for chlorogenic acid and K284 with CHI3L1 (PDB ID: 1NWR). A) Chlorogenic acid's binding site largely overlaps with a part of the binding site of K284. The chlorogenic acid molecule is shown in yellow, with red bonds indicating the presence of oxygen atoms. K284 is shown in green, with red and blue bonds indicating the presence of oxygen and nitrogen atoms, respectively. CHI3L1 is shown in light purple. B) 2D diagram of the binding of K284 to CHI3L1. The types of molecular interactions are indicated by dashed lines with different color codes.

restricted docking by centering the search on this region. This second approach produced a similar binding conformation with comparable affinity (-8.5 vs. -8.4 kcal/mol) and largely involved the same key catalytic residues. The fact that two independent docking protocols converged on the same functional site strongly suggests that our predicted binding mode is reproducible. This convergence reinforces our confidence that chlorogenic acid specifically targets the active site of CHIT1 and the chitin-binding domain of CHI3L1. Our *in silico* findings provide evidence of a molecular mechanism driving the health benefits of chlorogenic acid. The dual role of chlorogenic acid, involving direct enzyme inhibition for CHIT1 and signal disruption for CHI3L1, offers a new perspective for understanding this important dietary compound. It is important to acknowledge that our study is conducted entirely through computer modeling. It invites further experiments to confirm our computational predictions of chlorogenic acid's true target, which could eventually help to develop new therapeutic strategies.

MATERIALS AND METHODS

Data used

The 3D structures of the human chitinase CHIT1 (PDB ID: 1LQ0), the human chitinase-like protein CHI3L1 (PDB ID: 1NWR), the human acidic mammalian chitinase AMCase (PDB: 3FXY), the mouse chitinase-like protein CHI3L3 (PDB: 1VF8), the human neutrophil elastase (PDB ID: 3Q76) and the human neutrophil defensin 1 (PDB ID: 3GNY) were obtained from the Protein Data Bank (PDB) database (19). The 3D structures of the examined compounds were obtained from PubMed as SDF files, then converted to mol2 files using OpenBabel-2.4.1 reported by O'Boyle et al. (25).

Docking analysis

Molecular docking was performed by using AutoDockTools-1.5.7 reported by Trott and Olson (12). The docking analyses were initially performed as blind docking (**Figures 1, 3, and 4**). Subsequently, restricted docking was performed at the active region of CHIT1 and the chitin-binding domain of CHI3L1, which were identified as the best binding sites of chlorogenic acid during blind docking (**Figures 5-8**). For blind docking, all grid box sizes were set as x = 126, y =126, and z = 126. The grid spacing was 0.375 Å. The coordinate center parameters were as follows, 1NWR (x = -28.118, y = 12.024, z = 63.415); 1LQ0 (x = 75.364, y = 36.123, z = 38.972); 3Q76 (x = 108.707, y = 89.904, z = 49.431); 3GNY (x = 2.473, y = -35.402, z = -0.729). For restricted docking, grid box sizes were set as x = 60, y = 60, and z = 60, yielding a grid box approximately one-tenth of the blind docking grid box. The coordinate center parameters were as follows, 1NWR (x = 40.727, y = -1.863, z = 31.574); 1LQ0 (x = 73.22, y = 42.684, z = 40.81).

Data visualization

To show the protein residues that interact with chlorogenic acid, the docking results were opened in Discovery Studio 25.1.0.0 for visualization by 2D diagram (20). The residue information was then used in Pymol 2.6.2.0 to obtain the 3D diagram. The Vina score results were analyzed and plotted to make figures using Microsoft Excel. The chemical structures were drawn using Microsoft PowerPoint.

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