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Original Research Article

Anti-collagenase Potentials and ADME/Tox Analysis of Natural Phenolic Compounds from Aqueous Extract of *Chrysophyllum albidum* Fruit Parts: an *in silico* Evaluation

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ABSTRACT

Collagen is a popularly known elastic structural protein in the human body system, where it forms an integral part of support networks in the skin, hair, and nails. This study evaluated natural phenolic compounds from *Chrysophyllum albidum* aqueous fruit extract *in silico* as potential anti-collagenase inhibitors. The phenolic compounds present in the extract include quercetin, caffeic acid, chlorogenic acid, kaempferol, apigenin, catechin, and gallic acid. Schrodinger Maestro (v12.8) was used to carry out the molecular docking procedure of the phenolic compounds with collagenase. QikProp (Schrodinger Maestro v12.8) and the AdmetSAR 2.0 database were also used to predict the ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicity profiles, respectively. DFT analysis was conducted using Spartan10 software. Molecular docking results revealed that chlorogenic acid has the strongest binding affinity with collagenase (-9.367 kcal/mol) compared with other *C. albidum* phenolic compounds (caffeic acid: -8.114 kcal/mol; gallic acid: -7.200 kcal/mol; quercetin: -6.551 kcal/mol; kaempferol: -6.182 kcal/mol; apigenin: -5.436 kcal/mol; catechin: -5.347 kcal/mol) and reference compounds such as resveratrol (-5.333 kcal/mol), Vitamin C (-9.296 kcal/mol), Vitamin E (-3.073 kcal/mol), ursolic acid (-2.144 kcal/mol) (except arbutin; -9.518 kcal/mol). Furthermore, chlorogenic acid displayed good moderation for ADME/tox parameters and binding free energy value (MMGBSA) as investigated. DFT analysis confirmed the stability and molecular reactivity of the compounds. This study identifies chlorogenic acid, a natural phenolic compound in *C. albidum* aqueous fruit part extract, as a potential lead for skin anti-aging remedies, subject to further investigation.

Keywords: collagenase, skin, inhibitors, docking, phenolics, *Chrysophyllum albidum.*

Introduction

Skin aging is an inevitable biological process characterized by progressive degeneration of many physiological functions involving several tissues and organs in the human system, including the skin.[1,2] In the skin, collagen is a crucial structural protein that forms part of its building blocks. Furthermore, it confers an elastic nature on the skin while maintaining strength and flexibility.[1] Collagenase, a metalloproteinase enzyme, is known for degrading collagen in the extracellular matrix. As the skin goes through the subtle rigors of aging, reactive oxygen species accumulate to increase the activity of collagenase in the skin, resulting in progressive loss of skin tenacity and elasticity, causing visible skin wrinkles and sagging[3]. Skin aging is reportedly caused by light (photoaging) or age-related factors.[4] Degradation of the extracellular matrix has been heavily linked to collagenase activity.[5] Thus, collagenase, amongst other skin-aging enzymes, has been marked as a target for popular anti-aging cosmetic products.[6]

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Conventional skin cosmetics are formulated with synthetic compounds and other chemical substances and are not without harmful dark sides. Skin cancer and allergies are common side effects peculiar to the use of most cosmetics.[7] Furthermore, natural skin protection can be damaged by harmful chemicals, resulting in increased collagenase activity and, ultimately, collagen degradation.[8] Due to the increasing prevalence of the side effects related to the use of chemical-based skin cosmetics, the attention of the populace is shifting to using plant-based products, which emerge as cheaper and more effective alternatives. Plants are rich sources of antioxidants, including polyphenols, which are beneficial for maintaining skin health.[7] Natural plant compounds like cocoa polyphenols and epigallocatechin gallate have been reported to display anti-collagenase activity.[9] It was also reported that caffeine showed a comparatively good affinity with collagenase.[9] African star apple, *Chrysophyllum albidum*, is a highly nutritional plant popularly consumed in northern, southwestern, and eastern parts of Nigeria.[10,11] It is a seasonal fruit (December–April) rich in natural antioxidants (C and E) and has been reported to attenuate oxidative stress in disease conditions. Antioxidants play an essential role in boosting collagen production and ameliorating skin inflammation.[8] The edible part of *C. albidum* (fruit pulp) is rich in flavonoids, saponins, tannins, alkaloids, terpenoids, polyphenols, and other essential phytochemicals. In a previously reported study, polyphenolic constituents of *C. albidum* fruit parts (seed coat, flesh pulp, and back coat) were characterized and quantified using HPLC-DAD.[10,12] The output from the study revealed that the aqueous extract of *C. albidum* fruit parts contains polyphenols like gallic acid, cyanidin, catechin, caffeic acid, chlorogenic acid, quercetin, kaempferol, and apigenin (Table 1).[10] Computational (*in silico*) techniques are valuable for discovering novel compounds with therapeutic activity.[13,14] In recent times, computational techniques using artificial intelligence, deep learning, and machine learning have proven to be reliable in expediting drug discovery and drug design by enabling researchers to screen large libraries of compounds against therapeutic

targets within a short period. Molecular docking, a computer-aided drug design technique, has been effectively used to predict the binding modes of myriads of compounds possessing inhibitory properties against crucial protein targets.[15-17] Collagenase inhibition is a potent strategy for skin aging because it prevents collagen degradation, which is necessary to prevent wrinkle formation and keep the skin firm.[18] Previous studies have documented the use of various phytochemicals as anti-aging skin products.[9] However, there needs to be more information on the collagenase inhibitory potentials of *C. albidum* and its use as a possible alternative for conventional skin-aging therapy despite its good antioxidant profile.

This study aims to fill this knowledge gap by providing relevant information as a foundation for further *in vitro* and *in vivo* investigations into using *C. albidum* in skin-aging therapy. In the present study, the phenolic acids characterized from *C. albidum* fruit parts were screened for inhibition against collagenase *in silico* via molecular docking. Density functional theory (DFT) analysis was also performed to assess the stability and molecular reactivity of the phenolic acids. The pharmacokinetic properties (adsorption, distribution, metabolism, excretion, and toxicity) of the *C. albidum* phenolic acids were also evaluated to assess the compounds for drug-likeness and safety. Therefore, this study aimed to evaluate the anti-collagenase potentials of *C. albidum* fruit part phenolic acids as potential collagenase inhibitors and as potential hit compounds for skin anti-aging therapy using an *in silico* approach.

Materials and Methods

Maestro Schrodinger Suite (v12.8, 2021 release) was deployed as computational software for this study.

Protein crystal structure preparation
The Protein Preparation Wizard of Glide software in Maestro Schrodinger Suite (v12.8, 2021 release) was used to prepare the crystal structure of collagenase. The crystal structure of human collagenase (PDB ID: 1HFC) was retrieved from the RCSB-PDB (Protein Data Bank) database. The glide preparation protocol assigned zero bond orders to metals while hydrogen atoms were introduced to the structures. An optimization process was used to optimize hydrogen bond networks in the protein structure using PROPKA, thus refining the protein structure. Water molecules were also removed from the protein (waters with less than three hydrogen bonds to non-water molecules). Finally, restrained protein minimization was done using the Optimized Potentials for Liquid Simulations (OPLS4) force field to eliminate steric clashes.[19,20]

Table 1: Phenolic components of *C. albidum* fruit part aqueous extracts

Compounds	Extracts
Gallic acid	Flesh pulp, back coat
Catechin	Flesh pulp, seed coat
Chlorogenic acid	Flesh pulp, seed coat, back coat
Caffeic acid	Flesh pulp, seed coat, back coat
Quercetin	Flesh pulp, seed coat, back coat
Kaempferol	Flesh pulp, seed coat, back coat
Apigenin	Flesh pulp

Generation of receptor grid
A receptor grid file was generated to map the active site on the protein surface before the molecular docking procedure. The RGG panel of the Schrodinger software (v12.8, 2021 release) was used for the job. Active site mapping included marking the atoms of the co-crystallized compound present at the protein's active site selected in the project area. The coordinates for the grid were generated along the x, y, and z directions.[19]

Preparation of ligands
The LigPrep panel of Maestro Schrodinger software (v12.8, 2021 release) was used to prepare the ligands used in this study. The compounds used were documented in a study where *C. albidum* fruit parts (seed coat, flesh pulp, and back coat) were characterized.[10] They include gallic acid, quercetin, apigenin, kaempferol, chlorogenic acid, caffeic acid, and catechin (see Table 1). The 3D-chemical structures of the compounds were retrieved from the NCBI database (PubChem) (see Table 2). Irrelevant structures were eliminated while generating and optimizing variations of structures. The procedure converted the structures into low-energy forms suitable for docking. Using EpiK (Schrodinger Suite), the OPLS4 force field was deployed and left at the standard pH range (7.0 ± 2.0) to generate possible ionization states.[19]

Molecular docking using glide (extra precision)
The compounds from the aqueous extract of *C. albidum* fruit parts were docked into the active site of the prepared protein structure using Glide with extra precision (XP). The structures with the best binding poses were viewed, and the docking scores (binding affinity) were recorded.[19,21]

Binding free energy calculations (MM-GBSA)
Ligand-protein complexes generated from the molecular docking procedure were used for free energy calculation using the PRIME MM-GBSA (Molecular mechanics with generalized Born and surface area solvation) Panel (Schrodinger Suite). MM-GBSA uses energy calculations to quantitatively measure the energy differences in free and complex ligands and proteins after minimization. The OPLS4 force field was used while other factors were maintained.[22,23]

ADME/TOX analysis
ADME/Tox analysis was conducted using the QikProp Module of Maestro (v12.8, 2021 release) to determine the pharmacokinetic properties and drug-likeness (Lipinski's rule of five). In contrast, the AdmetSAR database was used to assess the toxicity profile.[19,23]

DFT analysis
DFT calculations (B3LYP functional method and 6-31G* basis set) were conducted on three hit compounds from *C. albidum* with high docking scores against collagenase using Spartan 10 computational chemistry software (version 1.1.0. Wavefunction, Inc. Irvine, CA. 2010).[24] A preliminary search for the best conformer distribution for each hit compound was conducted before the stable candidates were selected and subjected to the DFT analysis. The analytical parameters obtained from the quantum chemical calculation include the energy band gap (designated by E_g), which is the mathematical difference between E_{LUMO} and E_{HOMO} (frontier molecular orbitals), and other derived parameters (global reactivity descriptors), including ionization energy (I), electron affinity (A), chemical hardness (η), chemical softness (δ), and electronegativity (χ) (Olugbogi *et al.*, 2022). Ionization energy (I) and electron affinity (A) values were calculated using Koopman's theorem, while calculations for chemical hardness (η), chemical softness (δ), and electronegativity (χ) were derived using Parr and Pearson. Thermodynamic parameters (electronic energy, enthalpy, Gibb's free energy, and dipole moment) were also assessed.[24]

Results and Discussion

In this study, phenolic ligands from *C. albidum* were docked into the active site of collagenase. The resulting interactions between the ligands and collagenase are shown in Table 2. Chlorogenic acid, quercetin, kaempferol, and apigenin showed promising interactions with collagenase compared to the reference compounds (except arbutin). The resulting docking scores (binding affinities) and binding free energy values are displayed in Table 3. Chlorogenic acid had the highest docking score compared to the other *C. albidum* ligands, while quercetin, kaempferol, apigenin, and catechin displayed good binding free energy.

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Table 2: Molecular docking results for interaction between *C. albidum* ligands and collagenase

Compound	PUBCHEM ID	No of H-bonds	Interacting Residues/ H-bond distance (Å)
Arbutin	440936	6	SER239 (2.15), TYR237 (2.21), GLY179 (2.14), ARG214 (2.06), GLU219 (1.93), ASN180 (2.13)
Vitamin C	54670067	3	LEU181 (1.88), PRO238 (1.90), GLU219 (1.92)
EGCG	65064	3	GLU219 (1.60, 1.85), TYR240 (2.45)
Resveratrol	445154	2	LEU181 (2.14), ALA182 (1.86)
Vitamin E	14985	1	TYR240 (2.35)
Ursolic acid	64945	1	GLU219 (2.44)
Chlorogenic acid	1794427	5	GLU219 (1.92), TYR240 (2.77), GLU209 (1.80, 2.01), ALA182 (1.77)
Caffeic acid	689043	2	TYR237 (2.34), ARG214 (1.89)
Gallic acid	370	2	GLU219 (1.86), TYR237 (2.11)
Quercetin	5280343	4	TYR240 (2.61), GLU219 (2.04), ALA182 (2.01), ASN180 (2.32)
Kaempferol	5280863	4	TYR240 (2.57), GLU219 (2.19), ALA182 (1.93), ASN180 (2.17)
Apigenin	5280443	4	TYR240 (2.80), GLU219 (1.76), ALA182 (2.16), ASN180 (2.24)
Catechin	73160	2	GLU219 (2.14), ALA182 (1.82)

Table 3: Binding affinity and binding free energy of *C. albidum* phenolic compounds with collagenase

Compounds	Binding Affinity (Kcal/mol)	[a]ΔGBind	[b]$\Delta GBind_{Coulomb}$	[c]$\Delta GBind_{VDW}$	[d]$\Delta GBind_{Lipo}$	[e]$\Delta GBind_{HBond}$
Arbutin	-9.518	-12.46	-52.74	-13.56	-15.27	-5.19
Vitamin C	-9.296	7.38	-46.18	-5.47	-2.76	-3.89
EGCG	-5.755	-23.73	-32.38	-33.46	-10.63	-3.57
Resveratrol	-5.333	-24.9	-17.09	-22.54	-15.46	-2.04
Vitamin E	-3.073	-26.77	-12.71	-36.09	-18.68	-1.54
Ursolic acid	-2.144	37.73	31.2	-8.73	-14.26	-0.39
Chlorogenic acid	-9.367	-14.97	-32.41	-28.79	-15.22	-5.57
Caffeic acid	-8.114	-5.42	-27.78	-28.28	-11.28	-2.64
Gallic acid	-7.2	-1.2	-29.47	-17.89	-8.67	-2.14
Quercetin	-6.551	-26.26	-31.91	-31.64	-6.43	-2.65
Kaempferol	-6.182	-24.19	-26.87	-32.71	-6.95	-2.25
Apigenin	-5.436	-25.65	-25.01	-30.45	-4.73	-2.18
Catechin	-5.347	-25.8	-27.06	-28.23	-11.32	-2.29

[a]MMGBSA binding free energy (kcal/mol); [b]Contribution of the Coulomb energy to the MMGBSA free energy calculation; [c]Contribution of the van der Waal's energy to the MMGBSA free energy calculation; [d]Contribution of the lipophilic binding to the MMGBSA free energy calculation; [e]Contribution of the hydrogen bonding to the MMGBSA free energy calculation

Binding poses displaying the interaction of the *C. albidum* ligands with collagenase are displayed in Figures 1 – 3. Also, the results for the drug-likeness (Lipinski's rule of five) and pharmacokinetic properties of the *C. albidum* ligands were displayed in Table 4. In contrast, the druggability and toxicity profile (AdmetSAR) of the *C. albidum* ligands are displayed in Table 5. Molecular docking is a computational method widely accepted as a potent tool for evaluating different natural or synthetic compounds as potential hit compounds for many pharmacological applications.[25] It helps to obtain crucial information, which could give an understanding of the inhibitory nature of compounds by predicting their experimental binding modes.[21] The binding affinity, shown by the docking score, is expressed as a negative value in kcal/mol. Thus, strong interactions between the ligand and protein are depicted by lower negative values.[26] Collagenase is a metalloenzyme that has been marked as a captivating target for a plethora of anti-aging skin cosmetics.[3] Several plants have been screened *in vitro* for anti-collagenase activity as potential anti-aging remedies.[1,27] Their findings show that the plants with the most anti-collagenase activity were rich in polyphenols. The findings present phenolic-rich plant compounds as ideal plants for anti-collagenase activity, e.g., *C. albidum*.[10] Furthermore, some studies have also deployed an *in silico* molecular docking approach. For instance, caffeine was screened against collagenase for potential inhibitory activity using molecular docking.[3]

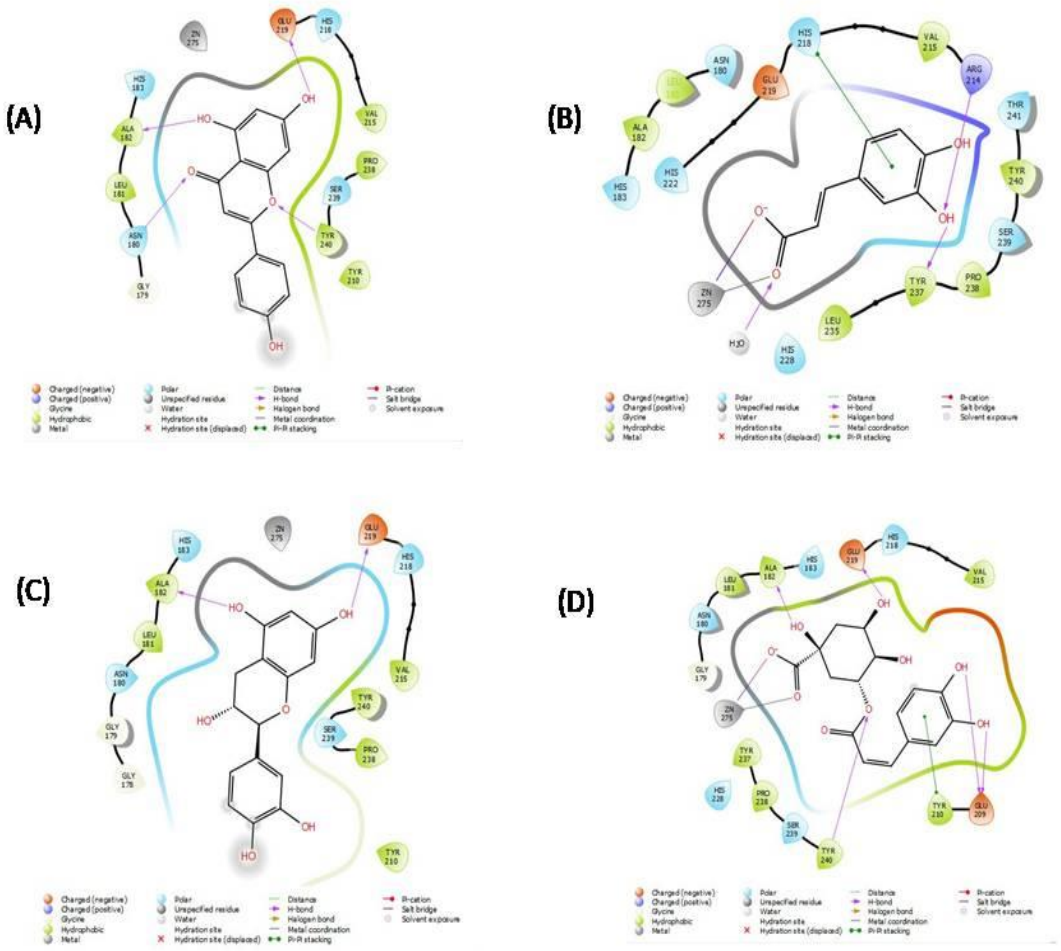

Figure 1: Binding poses of A) apigenin B) caffeic acid C) catechin D) chlorogenic acid with collagenase

In this study, Glide XP molecular docking was deployed to predict the binding affinity (docking score) of natural phenolic compounds from *C. albidum* with collagenase. Considerably, the procedure displayed favorable interactions between the *C. albidum* phenolic compounds and collagenase. Arbutin, epigallocatechin gallate, vitamin C, vitamin E, resveratrol, and ursolic acid were reference compounds. For maximum inhibitory action on enzymes, there must be an interaction between the ligand and one or more residues at the enzyme's active site.[22,25,28] The amino acid residues in the binding pocket of collagenase include GLY179, PRO238, TYR240, LEU181, ASN180, HIS218, and GLU219.

Table 2 displays the molecular docking results for the interacting residues of the respective *C. albidum* ligand-collagenase complexes. Interestingly, the *C. albidum* ligands formed hydrogen bond interactions with one or more residues. The images for the protein-ligand interactions between the *C. albidum* compounds and collagenase are displayed in Figures 1–3. It was also observed that the phenyl ring of some of the *C. albidum* compounds formed pi-pi bonds with collagenase. Pi-pi bonds have been marked as crucial factors in protein-ligand interaction as they contribute significantly to binding enthalpy.[22] Chlorogenic acid formed five (5) strong hydrogen bonds with interacting residues (GLU219, TYR240, GLU209, and ALA182) at the active site of collagenase. At the same time, arbutin showed the highest number of hydrogen bonds formed with interacting residues on the active site of collagenase (SER239, TYR237, GLY179, ARG214, GLU219, and ASN180). The hydrogen bond distances between chlorogenic acid and collagenase were found to be 1.92Å, 2.77Å, 1.80Å, 2.01Å, and 1.77Å. Two other *C. albidum* compounds (caffeic acid and gallic acid) also displayed promising interactions with collagenase.

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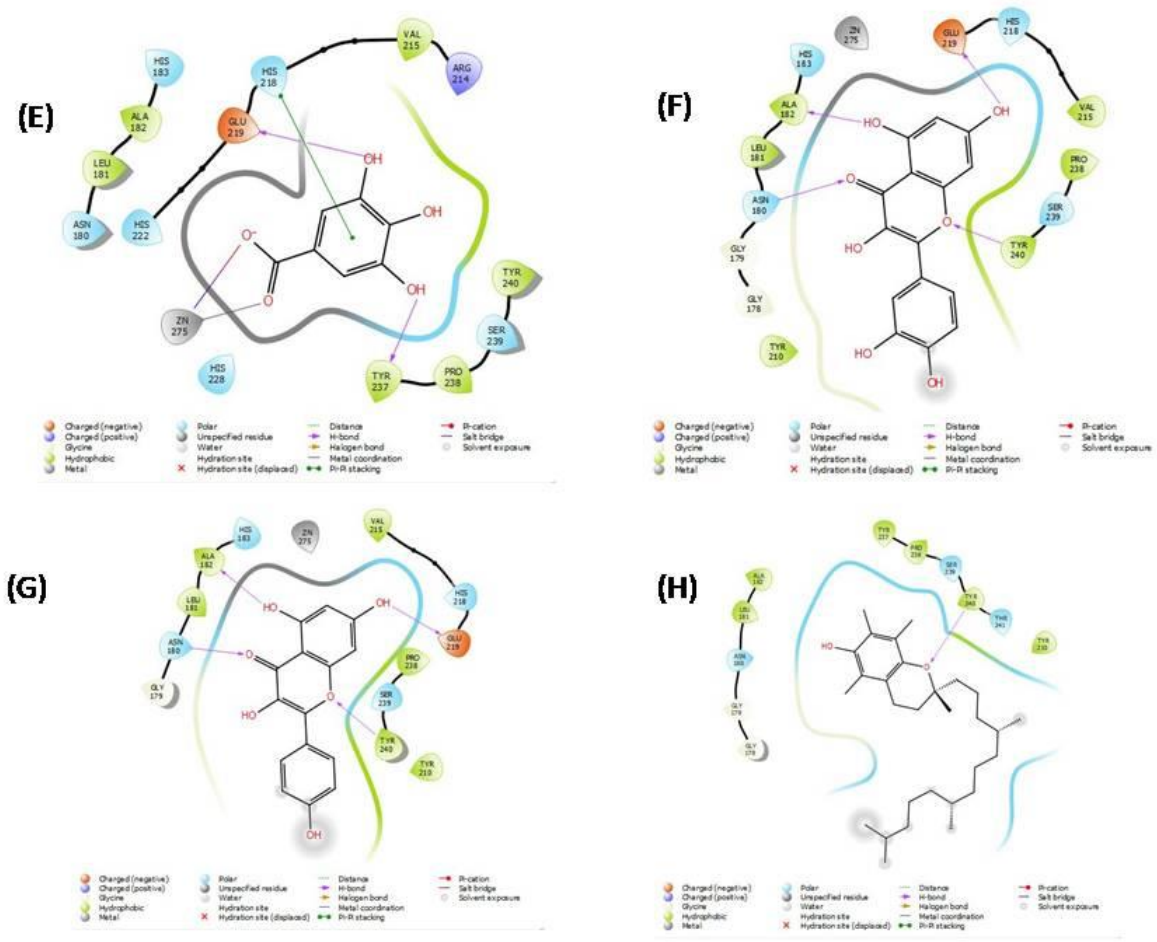

Figure 2: Binding poses of E) gallic acid F) quercetin G) kaempferol H) vitamin E with collagenase

The hydrogen bonding distance between caffeic acid and collagenase was observed to be 2.34Å and 1.89Å, while the bonding distances observed for gallic acid were observed to be 1.86Å and 2.11Å. Most of the *C. albidum* phenolic compounds interacted with the amino acid residues at the active site of collagenase. Based on these results, we suggest that chlorogenic acid showed a more favorable interaction with collagenase than all the reference compounds (except arbutin) and other *C. albidum* phenolic compounds. Furthermore, the range of docking scores observed by the *C. albidum* compounds is from -5.347 kcal/mol to -9.367 kcal/mol, with chlorogenic acid also showing the highest binding affinity for collagenase (Table 3). Caffeic acid, gallic acid, quercetin, and kaempferol also displayed promising binding affinities (-8.114 kcal/mol, -7.200 kcal/mol, -6.551 kcal/mol, and -6.182 kcal/mol, respectively) higher than the values for the reference compounds (EGCG at -5.755 kcal/mol; resveratrol at -5.333 kcal/mol; vitamin E at -3.073 kcal/mol; and ursolic acid at -2.144 kcal/mol). The only exception is in arbutin and vitamin C (-9.518 kcal/mol and -9.296 kcal/mol, respectively) for binding affinity values. This result suggests that the phenolic compounds from *C. albidum* may be enlisted as promising inhibitory agents for collagenase.

The MMGBSA post-docking procedure is one of the most recommended programs for binding energy assessment. The free energy calculation is obtained using solvation models and molecular mechanics calculations.[20,29] Due to the highly reproducible nature of the program, it is used to rank the affinity of ligands after they have formed a complex with a protein.[30] For the binding energy calculations, the primary energy contributors are van der Waals (ΔGvdw), Coulomb interaction (ΔGCoulomb), hydrogen bond (ΔGHbond), and lipophilic energy (ΔGsolLipo). These energy contributors improve the ligands' binding affinity to the protein's binding area.[20,29] From this study, we observed that the compounds with good docking scores also displayed good binding energy scores. Out of all the *C. albidum* phenolic compounds assessed in this study, quercetin showed the highest binding free energy (-26.26 kcal/mol), followed by catechin (-25.80 kcal/mol), apigenin (-25.65 kcal/mol), and kaempferol (-24.19 kcal/mol) (Table 3). Chlorogenic acid also showed a binding free energy value of -14.97 kcal/mol.

ADME/Tox studies assess the absorption, distribution, metabolism, and excretion of novel pharmaceuticals during lead optimization to predict their metabolic fates after introduction to the human system.[19] ADME/Tox assessment results of *C. albidum* phenolic compounds are displayed in Tables 4-5. The parameters assessed include molecular weight, number of hydrogen bond donors (DHB), number of hydrogen bond acceptors (AHB), predicted octanol: water partition coefficient (QPlogPo/w), predicted blood-brain barrier partition coefficient (QPLogBB), Lipinski's rule of five violations, prediction of binding to human serum albumin (QPlogKhsa), van der Waals surface area of polar nitrogen and oxygen atoms (PSA), blockage of HERG channels (QPlogHERG), MDCK (QPPMDCK), and Caco-2 cell permeability (QPPCaco). These parameters must be examined before drugs can be selected as leading candidates.[19,24]
Lipinski's rule of five is crucial in determining the druggability of lead compounds. According to the rule, compliant compounds may be more likely to be selected for clinical trials in pharmacological studies.[19]
The results show that *C. albidum* phenolic compounds complied with the Lipinski rule. All the compounds did not violate any of the rules, except chlorogenic acid, which showed one violation.

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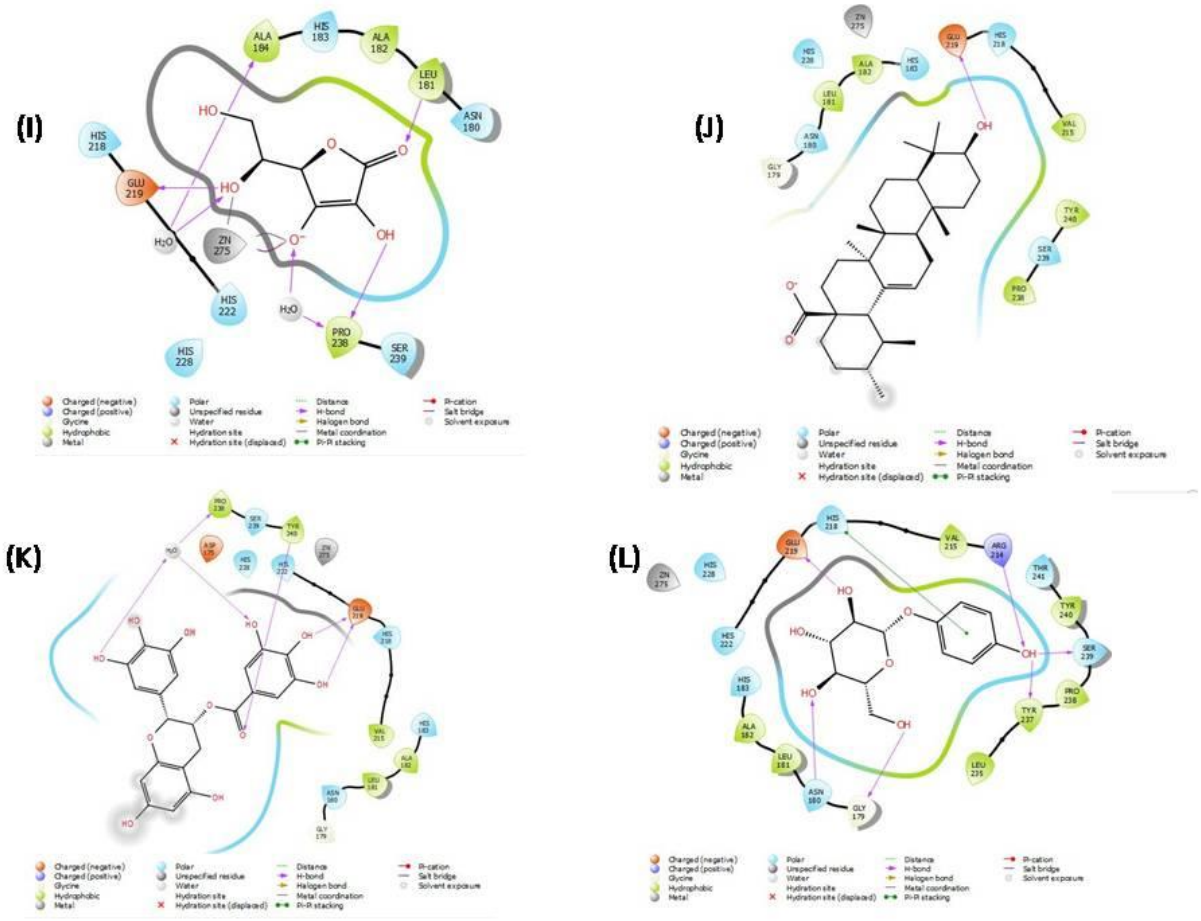

Figure 3: Binding poses of I) vitamin C J) ursolic acid K) epigallocatechin gallate L) arbutin with collagenase

As such, *C. albidum* phenolic compounds may be considered potential inhibitors of collagenase activity. From this study, it was observed that *C. albidum* phenolic compounds were in acceptance with the range of values indicated for molecular weight: DHB, AHB, QPLogBB, PSA, QPlogHERG, QPlogPo/w, and QPlogKhsa. However, only some compounds were observed to fall within the acceptance range for QPPMDCK and QPPCaco. Apigenin, kaempferol, and catechin displayed acceptable values for QPPMDCK, while only apigenin was within the acceptable range for QPPCaco. Furthermore, organ and genome toxicity assessments using the AdmetSAR database (Table 5) revealed that all *C. albidum* compounds have good potential for human intestinal absorption. Also, some of the *C. albidum* compounds may be highly toxic, with all the compounds falling within the class II and IV range for acute oral toxicity. According to the results, quercetin, kaempferol, and catechin could be potential inducers of mutagenesis. None of the *C. albidum* compounds tested positive for carcinogenicity and nephrotoxicity, although all compounds (except caffeic acid and catechin) also showed potential for hepatotoxicity.

Density functional theory (DFT) is a computational biology technique that uses quantum chemical calculations to predict the electronic structure, chemical properties, thermodynamic properties, molecular reactivity, and stability of chemical compounds.[24,31,32] The energy band gap refers to the difference between E_{HOMO} and E_{LUMO}.

HOMO and LUMO (frontier molecular orbitals), as shown in Table 6, describe the highest and lowest unoccupied electron orbitals of a compound. HOMO gives an insight into the nucleophilicity (electron-donating ability) of a compound, while LUMO projects the electrophilicity of a compound (electron-accepting ability) of a compound.[33,34] High HOMO and LUMO values indicate the high ability to donate and accept electrons, respectively, and vice versa. The frontier molecular orbital theory has been adopted as an effective way of predicting the chemical reactivity of compounds. Lower E_{LUMO} and higher E_{HOMO} values have been linked with high reactivity and low stability of molecules.[24] The E_{HOMO} values of the hit *C. albidum* compounds are ranked in increasing order as caffeic acid < chlorogenic acid < gallic acid. Gallic acid showed the highest E_{HOMO} value (-5.99eV), indicating a better tendency for nucleophilicity than chlorogenic acid and caffeic acid. The results also showed that gallic acid had the lowest E_{LUMO} value (-1.06eV) compared to the other compounds. The energy band gap result also showed that gallic acid had the highest energy band gap compared to chlorogenic and caffeic acid, indicating a more stable electronic configuration, reduced electron transition, and lesser reactivity. According to the literature, the energy band gap is crucial for predicting molecules' stability and chemical reactivity. Molecules are more stable, rigid, and less reactive when the energy band gap is more expansive.[24] However, the molecules are less stable and more reactive when the energy band gap is lower. The values for the energy band gap of *C. albidum* hit compounds are in the order chlorogenic acid < caffeic acid < gallic acid. Chlorogenic acid displayed the lowest band gap, indicating more effortless electron transfer and higher reactivity with the active site of collagenase than caffeic acid and gallic acid. Thus, chlorogenic acid shows a more significant potential for higher reactivity with collagenase active site and a more significant potential for collagenase inhibition than caffeic acid and gallic acid.

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Table 4: Drug-likeness and Pharmacokinetic Properties of *C. albidum* phenolic compounds

Compound	[a]M.wt	*[b]D.H.B	*[c]A.H.B	[d]QPlogPo/w	[e]QPLogBB	[f]Ro5	gQPlogKhsa	iQPLogHERG	jQPPMDCK	kQPPCaco	*hPSA
Caffeic acid	180.16	3	3.5	0.55	-1.555	0	-0.802	-2.191	22.104	10.218	95.859
Gallic acid	170.121	4	4.25	-0.572	-1.679	0	-0.984	-1.451	9.803	4.243	115.426
Apigenin	270.241	2	3.75	1.605	-1.446	0	-0.039	-5.114	114.487	47.531	99.755
Quercetin	302.24	4	5.25	0.367	-2.419	0	-0.343	-5.109	18.199	6.511	143.331
Kaempferol	286.24	3	4.5	1.041	-1.893	0	-0.191	-5.201	51.24	19.934	121.64
Catechin	290.272	5	5.45	0.451	-1.947	0	-0.419	-4.881	49.405	19.163	117.225
Chlorogenic acid	354.313	6	9.65	-0.229	-3.321	1	-0.913	-3.282	1.705	0.641	187.242

***M.wt –** Molecular weight; **D.H.B** – Donor hydrogen bond; **A.H.B** – Acceptor hydrogen bond; **Ro5** – Rule of Five; **PSA** – Polar surface area

[a]Molecular weight (range: 130.0 – 725.0); [b]Number of hydrogen bond donors (range: 0.0-6.0); [c]Number of hydrogen bond acceptors (range: 2.0-20.0); [d]Predicted octanol/water partition coefficient (range: -2.0-6.5); [e]Predicted blood brain barrier partition coefficient; [f]Lipinski's rule of five violations (maximum = 4), [g]Prediction of binding to human serum albumin (range: -1.5 -1.5); [h]Van der waals surface area of polar nitrogen and oxygen atoms (range: 7.0 – 200.0); [i]Predicted IC50 value for blockage of HERG K^+ channels (concern below -5); [j]Predicted apparent MDCK cell permeability in nm/sec (<25 is poor, >500 is very good); [k]Predicted Caco-2 cell permeability in nm/sec (<25 is poor, >500 is very good).

Table 5: Organ and genomic toxicity evaluation by AdmetSAR

Compound	A	B	C	D	E	F	G	H	I	J
Caffeic acid	-	-		+	-	+	-	+	-	+
Gallic acid	-	-		+	-	+	-	+	+	+
Apigenin	-	-		+	-	+	-	+	+	+
Quercetin	+	-		+	-	+	-	+	+	+
Kaempferol	+	-		+	-	+	-	+	+	+
Catechin	+	-		+	-	+	-	+	-	+
Chlorogenic acid	-	-		+	-	+	-	-	+	+

(+) = Active; (-) = Inactive**;**

***A** – Ames Mutagenesis; **B** - Carcinogenicity; **C** - Acute oral toxicity; **D** – Human intestinal absorption; **E** – Nephrotoxicity; **F** – Micronuclear; **G** – Eye Corrosion; **H** – Eye irritation; **I** – Hepatotoxicity; **J** – Androgen receptor binding**. Class I: fatal if swallowed (LD50 ≤ 5); Class II: fatal if swallowed (5 < LD50 ≤ 50); Class III: toxic if swallowed (50 < LD50 ≤ 300); Class IV: harmful if swallowed (300 < LD50 ≤ 2000); Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000) Class VI: non-toxic (LD50 > 5000)*

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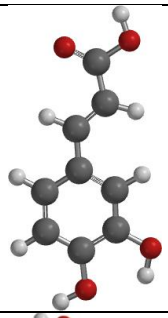
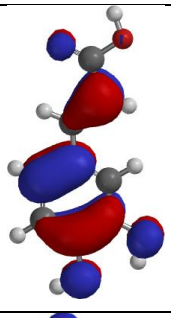
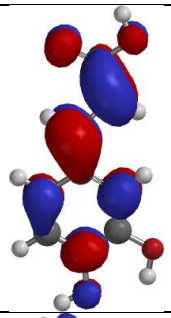
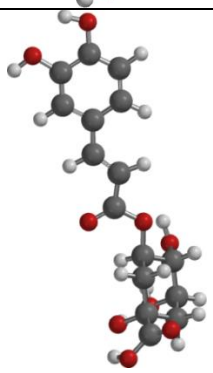
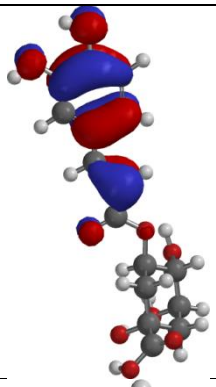
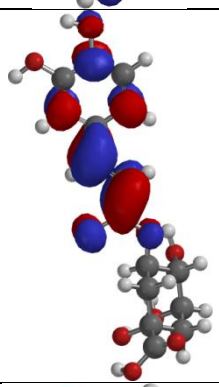
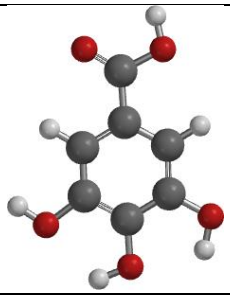
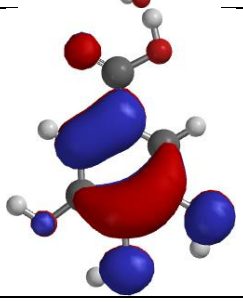
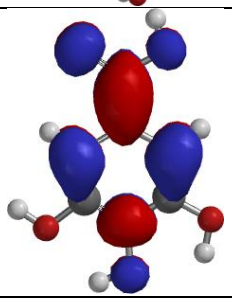
Table 6: The optimized structure of *C. albidum* hit compounds and their HOMO and LUMO

NAME OF COMPOUND	OTPIMIZED STRUCTURE	HOMO	LUMO
Caffeic acid			
Chlorogenic acid			
Gallic acid			

Molecules with higher ionization energy values have high stability and chemical inertness. Lesser ionization energy values indicate high reactivity and low chemical inertness.[35] From the results in Table 7, the order of ionization energy values is as follows: gallic acid > chlorogenic acid > caffeic acid. Caffeic acid showed the least ionization energy (5.86eV), indicating that it might be more reactive with collagenase than chlorogenic acid (5.95eV) and gallic acid (5.99eV). Electron affinity (*A*) refers to the energy released by adding an electron to a neutral molecule.[36] High *A* values indicate a higher predisposition to accepting electrons than molecules with lower *A* values. The order of electron affinity values is chlorogenic acid > caffeic acid > gallic acid. Chlorogenic acid has the highest electron affinity, suggesting higher reactivity with collagenase than caffeic acid and gallic acid. Chemical hardness (η) and chemical softness (δ) are indicators of a molecule's resistance to the deformation of an electron cloud.[24,37] Large energy band gap values are characteristic of rigid molecules, while low energy band gap values are characteristic of soft molecules. Furthermore, soft molecules tend to be more polarizable than complex molecules.[38] Gallic acid displayed the highest chemical hardness value (2.465eV), followed by caffeic acid (2.12eV) and chlorogenic acid (2.025). Chlorogenic acid also displayed the highest value for chemical softness (0.494eV-1), followed by caffeic acid (0.472eV^{-1}) and gallic acid (0.406eV^{-1}). The results show that chlorogenic acid has a higher potential for reactivity with collagenase than caffeic acid and gallic acid. Electronegativity (χ) depicts the electron-attracting ability of a molecule.[36] Chlorogenic acid has the highest electronegativity value (3.925eV) compared to caffeic acid (3.74eV) and gallic acid (3.525eV). This result indicates that chlorogenic acid attracts electrons from the collagenase active site more than caffeic and gallic acid. Thermodynamic analysis is vital for measuring the spontaneity of a given chemical reaction alongside its chemical stability.[24,39] The electronic energy (ground state) of chlorogenic acid, caffeic acid, and gallic acid was assessed in this study. Electronic energy gives information about the level of stability of a chemical structure.[17] Chlorogenic acid had the highest ground state electronic energy (-1297.754 a.u) compared to caffeic acid (-648.659 a.u) and gallic acid (-646.574 a.u), predicting that chlorogenic acid may have more chemical inertness due to its high stability. Enthalpy refers to the total energy of any given system. Whenever a ligand or molecule binds to an enzyme's active site, the system's energy change is depicted by the binding enthalpy. Chlorogenic acid, caffeic acid, and gallic acid have negative enthalpies and free energies, indicating that their binding with collagenase will be spontaneous. Furthermore, it depicts that the quality of the protein-ligand reaction between chlorogenic acid, caffeic acid, and gallic acid with collagenase will result from the amount of free energy available within the system. The results showed that chlorogenic acid had the highest enthalpy and free energy values, followed by caffeic and gallic acid. This result shows that chlorogenic acid would react more with collagenase than caffeic acid and gallic acid. The dipole moment is a crucial parameter that projects compounds' electron distribution and polarity.[24,40]

Table 7: Density functional theory parameters

Compounds	E_{HOMO} (eV)	E_{LUMO} (eV)	Eg (eV)	I((eV)	A(eV)	η (eV)	δ (eV-1)	χ (eV)
Chlorogenic acid	-5.95	-1.9	4.05	5.95	1.9	2.025	0.493827	3.925
Caffeic acid	-5.86	-1.62	4.24	5.86	1.62	2.12	0.471698	3.74
Gallic acid	-5.99	-1.06	4.93	5.99	1.06	2.465	0.40568	3.525

Table 8: Molecular weight, electronic energy, enthalpy, and dipole moment values for *C. albidum* hit compounds

Compound	Mol. Wt (a.m.u)	Electronic energy (a.m.u)	Enthalpy (a.u)	Gibbs Free energy (Hartree)	Dipole moment (Debye)
Chlorogenic acid	354.311	-1297.574	-1298.547	-1298.60	6.56
Caffeic acid	180.159	-648.679	-648.659	-649.70	4.29
Gallic acid	170.12	-646.495	-646.574	-647.60	2.41

High dipole moment improves hydrogen bond formation and binding interactions (bond and non-bond) with proteins. On top of that, good dipole moment values ensure compatibility of the molecule with the solvent medium.[17] Dipole moment results also showed chlorogenic acid having the highest value (6.56 Debye), which is highly desirable for good chemical reactivity with collagenase. The dipole moment values displayed by caffeic acid (4.56 Debye) and gallic acid (2.41 Debye) were also favorable for binding with collagenase.

Conclusion

The findings in this study suggest that *C. albidum* phenolic compounds displayed good binding ability and interaction with collagenase as potential inhibitors. Chlorogenic, caffeic, and gallic acid showed good binding affinity with collagenase. However, the present study highlights chlorogenic acid as a more suitable lead for collagenase inhibition due to its good binding affinity, stability, and reactivity with collagenase, as affirmed by DFT analysis. Chlorogenic acid should be further investigated via experimental methods to validate its anti-collagenase activity. It is also recommended that chlorogenic acid be optimized to cater to the potentially unfavorable toxicological properties highlighted in this study.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

All authors declare that the work presented in this article is original and that they will bear any liability for claims relating to the content of this article.

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