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Original Research Article

In Silico Investigations and Potential Approaches of *Tectona grandis* via Targeting MMP-9 for Triple Negative Breast Cancer

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ABSTRACT

The limited treatment options for triple-negative breast cancer are attributed to the absence of hormone receptor and human epidermal growth factor receptor 2 gene expression. There is a growing need to explore novel therapeutic drugs or combination therapies that can enhance the efficacy of Triple Negative Breast Cancer. *Tectona grandis*, with its antioxidant properties and potential health benefits, holds promise in cancer prevention and therapy. The objective of this research is to evaluate the potential of the bioactive substances of *T. grandis* as cancer drugs. The matrix metalloproteinase-9 structure was obtained from Protein Data Bank, while the substances derived from *T. grandis* were sourced from various existing studies and screened using PASS database, Lipinski's rule of five, and Veber rule. The molecular docking was performed using PyRx and visualized using PyMOL. ProteinsPlus and LigPlus were used to visualize the interaction between protein and ligand in a diagram. Twelve active substances of *T. grandis* leaves (butyl acetate, 4-hydroxy-4-methyl-2-pentanone, glycerin monoacetate, glycerin diacetate, methyl decanoate, sinapic acid, gallic acid, ferulic acid, P-coumarate, cinnamic acid, vanillic acid, and quercetin) show potential as anticancer agents based on PASS screening from Lipinski's rule of five and Veber rule. Among these, quercetin (-10), gallic acid (-7.3), and ferulic acid (-7.3) demonstrate the lowest binding energies according to molecular docking. Notably, quercetin exhibits the most favorable activity potential in PASS screening for both anticarcinogenic (0.757/0.007) and antineoplastic especially against breast cancer (0.577/0.012). Quercetin demonstrated the highest potential to work as a Matrix Metalloproteinase-9 inhibitor.

Keywords: Matrix Metalloproteinase-9, Quercetin, *Tectona grandis*, Triple Negative Breast Cancer.

Introduction

Breast cancer ranks as the second leading cause of cancer-related mortality, accounting for 9.6% of deaths, and represents the most prevalent form of new cancer cases worldwide, comprising 11.7% of all cases.[1] Among the diverse subtypes of breast tumors, triple negative breast cancer (TNBC) stands out as a distinct category characterized by the absence of hormone receptor expression and the amplification of Human Epidermal Growth Factor Receptor 2 (HER2) gene. As a consequence, TNBC patients typically face an unfavorable prognosis and limited options for therapeutic interventions.[2]Hormonal therapy is ineffective in TNBC cases due to the absence of hormone target receptors, leaving surgery and chemotherapy, either as standalone approaches or in combination, as the primary treatment modalities.

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Current therapeutic strategies for TNBC management revolve around targeting various aspects of the disease, such as DNA repair complexes (e.g., platinum compounds and taxanes), p53 pathways (taxanes), cell proliferation (regimens containing anthracyclines), and specific molecular targets. However, several studies have identified specific receptors that serve as potential targets for the development of novel therapeutic drugs, suggesting new avenues for improved treatment options.[3]

Tumor cells have the ability to secrete specific types of proteinases, namely serine proteinases, aspartic proteinases, cysteine proteinases, and matrix metalloproteinases (MMPs), which primarily influence the invasion and metastasis of tumors.[4] Among the various MMPs associated with cancer, particular attention has been directed towards the gelatinases due to their heightened expression in diverse malignant tumors and their correlation with tumor aggressiveness and unfavorable prognosis. Increased levels of MMP-9 have been observed in breast, brain, ovarian, pancreas, colorectal, bladder, prostate, and lung cancers. Activated gelatinases possess the ability of degrading various constituents of the extracellular matrix (ECM) as well as non-matrix proteins. Furthermore, gelatinases assume significant yet indirect roles in cellular signalling by regulating the availability and activity of molecules that target specific receptors involved in cellular growth, migration, inflammation, and angiogenesis. The activity of gelatinases can induce the release of latent information embedded within the ECM, thereby promoting cell migration and angiogenesis. Additionally, MMP-9 is capable of releasing ECM-sequestered factors such as

Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor- β (TGF-β), which stimulate the proliferation and migration of endothelial cells, ultimately facilitating angiogenesis and tumor growth.[5]

The effectiveness of chemotherapy is hindered by both drug-induced toxicities and resistance, specifically multiple drug resistance (MDR). Consequently, there is a pressing need to explore and develop novel therapeutic drugs and/or combination therapies as a means to mitigate toxicity and enhance efficacy in the treatment process.[6] *Tectona grandis*, widely recognized as a medicinal plant indigenous to South and Southeast Asia, particularly India and Indonesia, holds significant potential in this regard.[7] Notably, various components of this plant, including its leaves, encompass a plethora of secondary metabolites which exhibit diverse activities such as antibacterial, antitoxic, and antioxidant properties.[8,9] Antioxidant compounds are crucial health-protecting elements that play an important role in cancer prevention and therapy.[10] Hence, the investigation employed the molecular structure of MMP-9 from Protein Data Bank and ligands sourced from the PubChem database. Multiple computational simulations and screening including molecular docking analysis were utilized to scrutinize the interactions between MMP-9 and various chemical compounds. The aim of this research is to determine the influence of potential active ingredients or chemical compounds cposeapable of acting as inhibitors with anticancer properties against MMP-9. Ultimately, this study holds the potential to improve the advancement of *Tectona grandis* active substances as effective MMP-9 inhibitors, thereby contributing to the field of drug development.

Materials and Methods

Sample Retrieval

The structure of human matrix metalloproteinase (MMP-9), a three-dimensional model (3D model), was obtained from the Protein Data Bank in .pdb format, with a specific protein (1L6J). This model, originating from *Homo sapiens* organism, exhibits a favorable resolution of 2.15 Å and is characterized by the absence of mutations. Additionally, the target protein's 3D structure underwent sterilization through the utilization of PyMOL, resulting in the removal of the original ligand. The information regarding the active substances found in *Tectona grandis* was sourced from the studies conducted by Suryanti et al. (2020),[9] Murukan and Kumara (2018),[11] and Nayeem and Karvekar (2010).[12] To evaluate the activity of other MMP-9 inhibitors, Marimastat was employed as a reference compound.[13] The structure data format (.sdf) for the substances and Marimastat were obtained from the PubChem database.

Virtual Screening

Twenty-six substances derived from *Tectona grandis*, obtained from various studies, underwent screening to evaluate their potential anticancer effects using Prediction of Activity Spectra for Substances (PASS) database (http://www.way2drug.com/passonline/index.php). Lipinski's rule of five and Veber rule were applied to evaluate their drug-like molecular properties of SwissADME (http://www.swissadme.ch/index.php). The process of identifying small molecules within MMP-9 involved molecular docking analysis with AutoDock Vina on PyRx. The accuracy of the docking method was evaluated by comparing the binding energy of the lead substances with a reference ligand. However, it is important to consider other parameters such as LogP, hydrogen bond acceptors, hydrogen bond donors, the number of rotational bonds, and the volume of the molecule.

Molecular Visualization

The visualization process was carried out utilizing PyMOL, a molecular graphics tool that is widely recognized for its cross-platform capabilities in visualizing three-dimensional (3D) representations of proteins, nucleic acids, small molecules, electron densities, surfaces, and trajectories.[14] This software was employed to generate visual representations of the docking results and the 3D structure of the target protein, as well as to modify data annotations for the molecules. The visualization procedure entailed presenting the 3D protein structure in both animated and surface forms.

Results and Discussion

Lipinski's rule of five (RO5), a set of guidelines used to evaluate the drug-likeness of chemical substances with specific biological activity for oral administration, plays a significant role in cancer drug design and targeting. It not only aids in assessing the drug's physicochemical properties but also enables the evaluation of its toxic characteristics.[15] Adhering to the RO5 guidelines, an optimal drug molecule should have a molecular weight of below 500 g/mol, a log P value of below 5 (indicating hydrophobicity), a maximum of 5 hydrogen bond donors (with an optimum of 2), and a maximum of 10 hydrogen bond acceptors (with an optimum of 5).[16] Additional research has introduced two supplementary criteria, a polar surface area (PSA) of equal to or less than 140 Å and fewer than 10 rotatable bonds (RB) which exhibit a correlation with the permeability and flexibility of drugs.[17] Bioavailability Radar was employed to swiftly evaluate the drug-likeness, considering six key physicochemical properties: lipophilicity (XLOGP3: -0.7 to +5.0), size (molecular weight: 150 to 500 g/mol), polarity (TPSA: 20 to 130 Å2), solubility (log S < 6), saturation (fraction of carbons in sp3 hybridization not less than 0.25), and flexibility (with no more than 9 rotatable bonds).[18] The bioavailability radar imaging presented in Figure 1 demonstrates that the substances derived from *Tectona grandis* generally conform to the acceptable range, with the exception of cinnamic acid, ferulic acid, gallic acid, p-coumarate, quercetin, sinapic acid, and vanillic acid. These substances exhibit a high saturation index (INSATU), indicating a significant level of unsaturation within their molecular structures. This high INSATU value is associated with reduced solubility and poor bioavailability. Consequently, delivering these drugs to their intended site of action becomes challenging, potentially compromising their effectiveness.[19] The application of Lipinski's rule of five (RO5) and Veber rule to the chemical substances in *Tectona grandis* led to a finding that 12 substances demonstrated promising biological activities and met all the criteria of RO5 and Veber rules, indicating their drug-like nature (Table 1).

The interactions between target proteins and drug-like compounds were predicted using the PASS database, which is a popular approach to analyze structure-activity relationships applied practically in all pharmaceutical firms. In order to identify the compounds and indicate whether they are active or inactive, PASS provides the crucial bioactivities of the chemical compounds as Probable activity (Pa) and Probable inactivity (Pi) values.[20] The prediction showed that quercetin had the highest probabilities of anti-carcinogenicity (0.757/0.007) and antineoplastic activity, especially in breast cancer (0.577/0.012). P-coumarate, on the other hand, showed no results because of its molecular charge of -1. After being screened for their drug potential abilities, the active substances entered the next stage, which is analysis of the binding affinity of target protein. The chemical substances derived from *Tectona grandis* were taken as ligands, while marimastat served as the standards, and MMP-9 was used as the target. The docking simulations were performed by maximizing the Vina Search Space in PyRx (grid docking centers X = 36.8817, Y = 38.8437, Z = 34.6209; dimensions X = 48.3649 Å, Y = 78.6125 Å, Z = 66.4490 Å). The simulation results showed the binding energy of *Tectona grandis*-derived substances against MMP-9. Quercetin was found to be the substance with the lowest binding energy (Table 3). The attainment of the lowest binding affinity is crucial in the context of inhibition as it signifies a robust interaction between the ligand and the target protein, thereby facilitating effective inhibition.[21] Ligands with the most negative binding energy can be predicted as the most potential MMP-9 inhibitor. MMP-9 was used in this study because it is a crucial enzyme in cancer due to its proteolytic activity, which plays a key role in the development of tumors by regulating cancer cell migration, epithelial-to-mesenchymal transition, survival, immune response induction, angiogenesis, and tumor microenvironment formation.[22] The docking data were molecularly visualized using PyMOL for the purpose of staining and structural selection (Figure 2).

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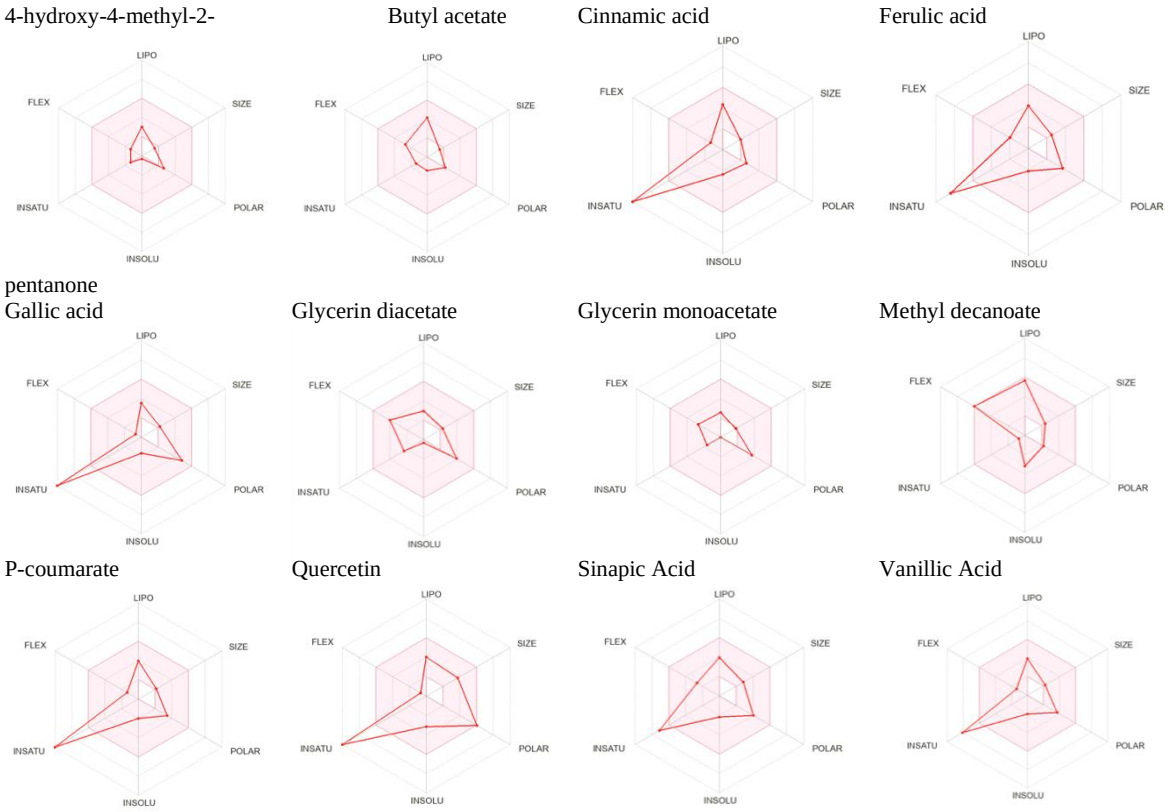

Figure 1: The Bioavailability Radar Diagram of *Tectona grandis* Derived Chemical Substances. The pink region denotes the ideal range for every characteristic

Table 1: Outcomes of Protein Prediction Using Substances Derived from *Tectona grandis*

Substance	Lipinski Rule of Five				Veber Rule	
	Molecular Weight (g/mol)	H-bond Acceptors	H-bond Donors	Lipophilicity (LogP)	Rotatable Bonds	TPSA (Å^2)
Butyl acetate	116.16	2	0	1.53	4	26.30
4-hydroxy-4-methyl-2-pentanone	116.16	2	1	0.63	2	37.30
Glycerin monoacetate	134.13	4	2	-0.46	4	66.76
Glycerin diacetate	176.17	5	1	0.17	6	72.83
Methyl decanoate	186.29	2	0	3.36	9	26.30
Sinapic acid	224.21	5	2	1.31	4	75.99
Gallic acid	170.12	5	4	0.21	1	97.99
Ferulic acid	194.18	4	2	1.36	3	66.76
P-coumarate	163.15	3	1	1.35	2	60.36
Cinnamic acid	148.16	2	1	1.79	2	37.30
Vanillic acid	168.15	4	2	1.08	2	66.76
Quercetin	302.24	7	5	1.23	1	131.36
Marimastat (Reference)	331.41	5	5	0.65	11	127.76

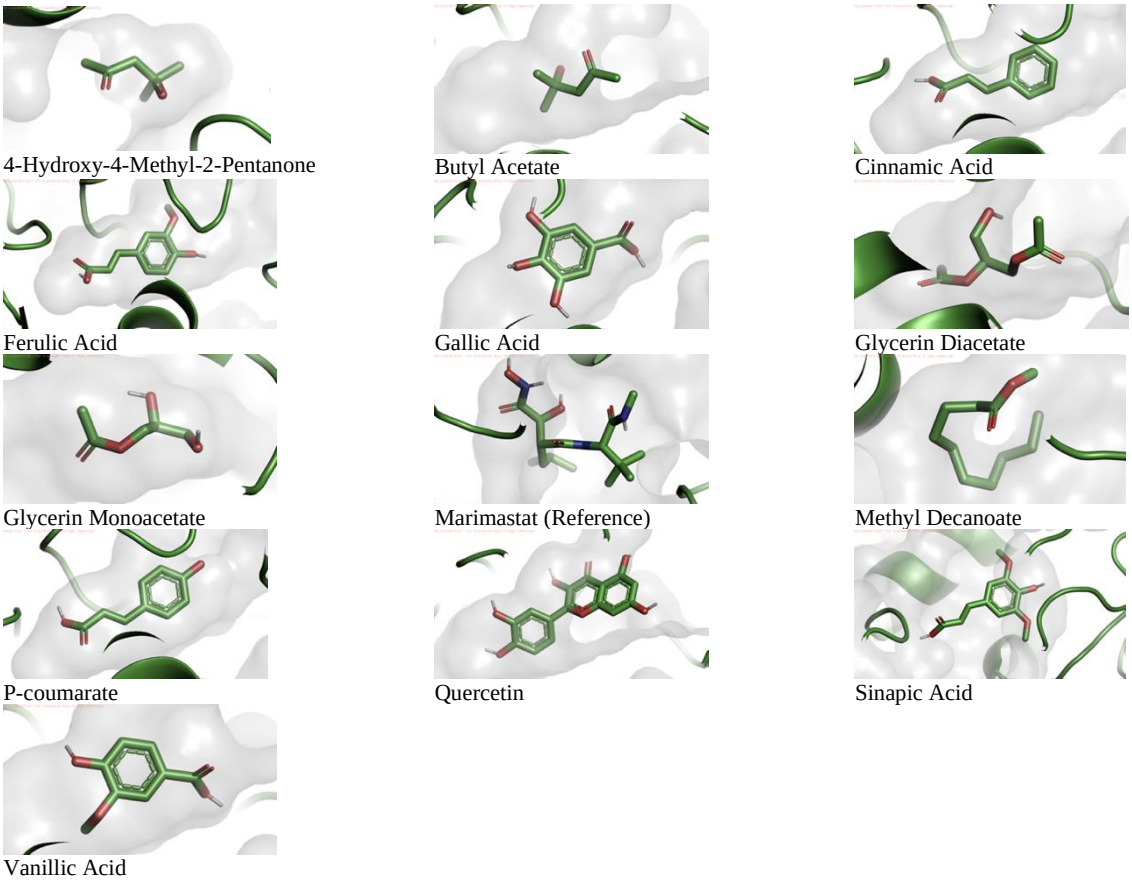

Figure 2: Binding of *Tectona grandis* Bioactive Substance and MMP-9. Molecular visualization using PyMOL software

The target protein was rendered as a translucent surface with an animated structure for visualization purposes. The substances exhibiting the lowest binding energy with the target protein were thoroughly investigated to elucidate the molecular interactions and visualize the types of the formed bonds. This analysis was performed using PoseView in ProteinsPlus' web portal (https://proteins.plus/). PoseView, a powerful computational tool, facilitates the generation of diagrams depicting protein-ligand complexes and enables the analysis and comprehension of molecular interactions while employing a fast tree re-arrangement algorithm to generate atomic resolution diagrams with minimized crossing lines and consistent residue layouts for related complexes.[23,24]

The diagrams made with PoseView conform to the chemical drawing conventions and provide an efficient and accurate way to visualize protein-ligand interactions. The direct bonds between the protein and ligands are denoted by dashed lines, whereas the interplaying protein residues and ligands are illustrated in the structural diagrams. The spline sections represent the hydrophobic portions of the ligands, and the communicating amino acids represent the hydrophobic interactions. To derive the structural diagrams and modify their layouts, the 2D drawing package is utilized. The residues forming directed interactions to the ligand were drawn as structure diagrams like the ligand, while all residues that are not involved in direct interactions were depicted as lines.[24,25] The 2D illustration of a complex generated by PoseView is termed a Pose Diagram, while the arrangement of the components is referred to as a Pose Layout.[25]

Quercetin and MMP-9 interact via hydrophobic contacts at Thr426A and Tyr423A, and form hydrogen bonds at Pro430A and Met422A.Hydrophobic interactions, characterized by the close proximity between non-polar amino acid side chains of the protein and lipophilic groups on the ligand, exerted a crucial influence in the stabilization of ligands at the binding interface.[26] Moreover, these interactions significantly contributed to the binding affinities between ligands and receptors. By virtue of their short-range attractive nature, hydrophobic interactions had the capacity of affecting the binding affinity through an effective stabilization of ligands at the binding interface.[27]

Hydrogen bonds played a pivotal role in the regulation of molecular interactions and exerted a significant influence on the binding affinity between proteins and ligands, thereby facilitating a wide range of cellular functions. By engaging in donor-acceptor pairings, hydrogen bonds effectively governed molecular interactions and promoted the enhancement of receptor-ligand interactions. Particularly, when both donor and acceptor exhibit substantially stronger or weaker hydrogen bonding capabilities in comparison to the hydrogen and oxygen atoms of water, hydrogen bonds could further reinforce the interactions between receptors and ligands. Additionally, hydrogen bonds possessed the ability of strengthening the affinity of ligand binding by displacing water molecules that are bound to the protein and redirecting them into the bulk solvent.[28]

MMP-9 engaged in interactions with the top three ligands, namely quercetin, ferulic acid, and gallic acid, as revealed by molecular docking analysis. Remarkably, both ferulic acid and gallic acid demonstrated equivalent binding affinity values. As presented in Figure 4, quercetin establishes bonds with four specific amino acid residues (Met422, Tyr420, Pro429, Arg424). Likewise, gallic acid formed five bonds with amino acid residues (Tyr420, His401, Thr426, Arg424, Ala417). In contrast, ferulic acid only formed a bond with a solitary amino acid residue (Glu402). Notably, hydrogen bonds were observed between the ligands and the target protein in all identified ligands.

Quercetin shows promise as a potential drug candidate for the treatment of cancer, particularly in anti-migration therapies.[29,30] Its ability to bind to MMP-9 with the lowest binding energy and to interact through hydrogen and hydrophobic bonds (Figure 3) makes it an attractive option. Furthermore, quercetin adheres to Lipinski's rule of five and Veber's rules, indicating that it possesses drug-like properties (Table 2). To deepen our understanding of the therapeutic properties and efficacy of these ligands, conducting *in vivo* and *in vitro* studies is highly recommended.

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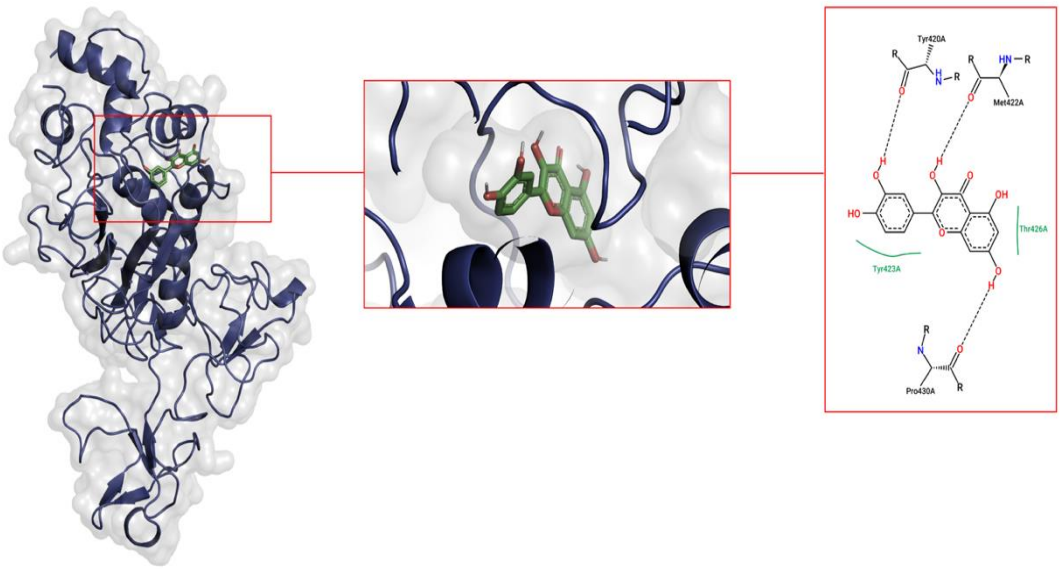

Figure 3: The protein target MMP-9 and its chemical interactions with quercetin were depicted in the structural visualization. The structure of MMP-9 was visualized using transparent and animated surfaces, and the PyMOL software was utilized for staining to distinguish between the protein and ligand

Table 2: Results of PASS Prediction

Substance	Prediction	Pa	Pi
Butyl acetate	Antineoplastic (breast cancer)	0.163	0.124
	Anticarcinogenic	0.333	0.047
4-hydroxy-4-methyl-2-pentanone	Antineoplastic (breast cancer)	0.464	0.083
	Anticarcinogenic	0.311	0.054
Glycerin monoacetate	Antineoplastic (breast cancer)	0.193	0.098
	Anticarcinogenic	0.392	0.032
Glycerin diacetate	Antineoplastic (breast cancer)	0.180	0.108
	Anticarcinogenic	0.459	0.023
Methyl decanoate	Anticarcinogenic	0.295	0.060
Sinapic acid	Antineoplastic (breast cancer)	0.462	0.023
	Anticarcinogenic	0.616	0.012
Gallic acid	Antineoplastic (breast cancer)	0.176	0.110
	Anticarcinogenic	0.395	0.031
Ferulic acid	Antineoplastic (breast cancer)	0.467	0.023
	Anticarcinogenic	0.616	0.012
Cinnamic acid	Antineoplastic (breast cancer)	0.300	0.055
	Anticarcinogenic	0.459	0.023
Vanillic acid	Antineoplastic (breast cancer)	0.298	0.055
	Anticarcinogenic	0.413	0.029
Quercetin	Antineoplastic (breast cancer)	0.577	0.012
	Anticarcinogenic	0.757	0.007

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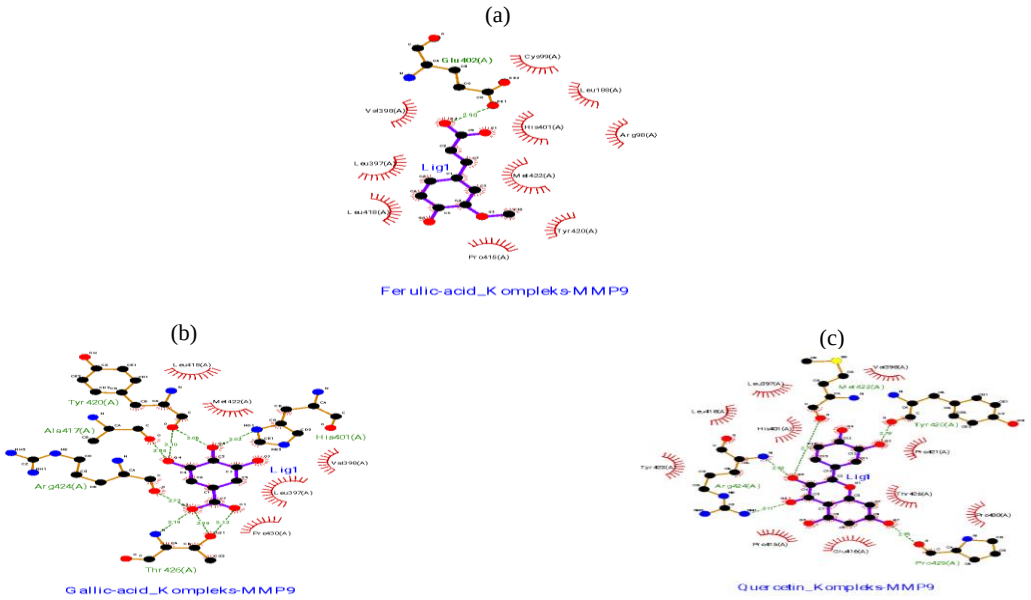

Figure 4: The Interactions between MMP-9 and Ferulic Acid (a), Gallic Acid (b), and Quercetin (c). Visualization through a Two-Dimensional Diagram Generated using LigPlus software

Table 3: Molecular Docking Outcome

Ligand	Target	Binding Affinity (kcal/mol)
Marimastat (Reference)		-6.8
4-hydroxy-4-methyl-2-pentanone		-4.7
Butyl acetate		-5.3
Cinnamic Acid		-6.9
Ferulic Acid		-7.3
Gallic Acid		-7.3
Glycerin Diacetate	MMP-9	-5.8
Glycerin Monoacetate		-4.3
Methyl decanoate		-4.6
P-coumarate		-7
Quercetin		-10
Sinapic Acid		-6.3
Vanillic Acid		-5.8

Conclusion

Quercetin demonstrated the highest potential to work as MMP-9 inhibitor. Lipinski's rule of five and Veber rules, along with molecular analysis and chemical interaction evaluation, was applied to assess the noteworthy stability of quercetin during molecular docking analysis. One limitation associated with quercetin is its high saturation level, which has the potential to impede drug delivery mechanisms and which might compromise its therapeutic efficacy. Additional investigations are needed to determine the precise atoms involved in the binding of proteins and ligands. To enhance our comprehension of the therapeutic properties and the effectiveness of these ligands, it is highly recommended to conduct further *in vitro* and *in vivo* studies.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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