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Computational Design of Herbal Inhibitors of PAI-1 for Accelerated Wound Healing

Ankita Sharma[1], Ozkan Fidan[2], Mohammed Er-rajy[3] and Mohamed El Fadili[3*]

[1]*Chitkara college of Pharmacy, Chitkara University, Rajpura-140401, Punjab, India.*
[2]*Department of Bioengineering, Faculty of Natural and Life Sciences, Abdullah Gül University, 38080, Kayseri, Turkey.*
[3]*LIMAS Laboratory, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University, Fez, Morocco.*

[*]mohamed.elfadili@usmba.ac.ma (Corresponding Author)

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ABSTRACT

Background: Wounds are one of the significant health issues that can cause serious complications if left untreated. The proper management and treatment of wounds is highly essential to avoid the chances of developing infections and therefore promote timely healing. Plasminogen activator inhibitor-1 (PAI-1) is a potential therapeutic target that interrupts the activation of plasminogen in the wounded tissues required for the healing process and therefore delays the healing process. Plant-based therapeutics are always demanded for wound healing because of their potential efficacy, optimized pharmacokinetics, safety, and availability.

Purpose: The aim of the current study is to identify potent plant-based molecules for wound healing and to understand the most probable underlying mechanisms of action for the same.

Methods: Thus, a library was prepared consisting of eighty-five plant-based ligands derived from diverse plants such as aloe vera, turmeric, neem, ginseng, calendula, etc., which were traditionally used for the management of wounds and related issues.

Results: Therefore, the prepared ligand library is computationally screened against a three-dimensional model of PAI1 to shortlist the potential leads, followed by molecular dynamic simulation to validate their thermodynamic stability. The resulting simulations of the PAI1-emodin complex over a 100 ns period revealed their high stability.

Conclusion: Thus, emodin was proposed as a potential inhibitor of PAI1 and can be used to develop a newer wound healing agent.

1. Introduction

Wounds that are partially treated or left untreated may lead to serious health complications that may be life-threatening in nature. A wound can be defined as a cut, opening, or injury in the skin tissue that can be caused as a result of trauma, surgery, or an underlying medical disorder. The severity of these wounds may range from minor cuts and scratches to more serious injuries, including burns or deep lacerations (Movaffagh *et al.*, 2022; Mujwar, 2021a; Wang *et al.*, 2023). Wounded tissues have the potential for causing infection regardless of the size and severity and therefore require proper treatment to avoid any further health consequences. Health problems associated with wounds, like delayed healing, chronic discomfort, tissue damage, and sepsis, may lead to potentially fatal infections in case of inefficient therapy. Thus, the wounds have a significant social and economic impact, resulting in compromised quality of life with increased healthcare costs (Almaieli *et al.*, 2023; Mujwar & Pardasani, 2022; Patel *et al.*, 2019).

The proper management of a wound is a critical process, including the use of appropriate therapeutics to promote quick healing, antibiotics for preventing infections, providing suitable dressings at regular time intervals, and accompanying debridement of damaged wounded tissues. Therefore, these critical aspects for the wound management are essential to prevent severe medical complications as well as timely healing by adequate management of wounded tissues and their associated complications (Mujwar & Kumar, 2020; Pathan & Williams, 2012; Wu *et al.*, 2019).

The World Health Organization (WHO) has considered wounds as a serious health concern, as millions of people worldwide are affected by wounds and related complications. A report released by WHO has revealed that every year more than 17 million people are affected by a varied range of wounded injuries. Low- and middle-income countries with limited resources for proper healthcare facilities for wound care lead to the permanent disabilities and morbidity in the wounded people. Wounds are responsible for around 1-2% of the worldwide disease burden as per

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the report released by WHO (Abazari *et al.*, 2022; Álvarez-Santos *et al.*, 2022; Winarni *et al.*, 2022).Wound-related diseases have a physical, social, and economic impact on human health globally. The cost of wound management may vary from several hundred to several thousand dollars per wound depending upon the severity of the wound and the duration of therapy for complete healing. Chronic pain, limited mobility, and psychological distress are other ways in which wounds can diminish an individual's quality of life. Therefore, wounds are a major health concern that requires intense and effective care for quick recovery to avoid severe complications. The majority of wounds can be effectively addressed by providing proper care and timely treatment for lowering morbidity and mortality and improving the quality of life for affected persons (Abdel-Mohsen *et al.*, 2020; Mujwar & Pardasani, 2015; Polaka *et al.*, 2022; Sharma *et al.*, 2021).

The plant-based herbal therapeutics have numerous advantages, like high effectiveness, comparative safety, easy accessibility, and economical prices over other sources. There, because of the above said reasons, the researchers are attracted towards the development of plant-based herbal therapeutics to counter the diseases affecting mankind by applying precise research to understand the involved mechanism of action of these plant-based natural substances (Fidan *et al.*, 2022; Mujwar *et al.*, 2022; Mujwar & Harwansh, 2022; Sharma *et al.*, 2021). Various plant extracts and preparations are used in traditional medical practices to promote healing, reduce inflammation, and prevent infections. A variety of plant species have been recognized to hold the potential for healing wounds effectively. Aloevera, Gotu kola (Centella asiatica), Bay, Burdock, Ginseng, Neem, Turmeric, Calendula, Terminalia arjuna, and German chamomile are a few examples of such plant species. Active constituents like polyphenols, terpenoids, and flavonoids show anti-inflammatory, antibacterial, and antioxidant properties in these plants (Agrawal *et al.*, 2021; Kumari *et al.*, 2024; Pradhan *et al.*, 2015; Singh *et al.*, 2019; Soni *et al.*, 2015).

Plasminogen activator-1 (PAI-1) is an important protein that regulates the fibrinolytic system and is known to be in charge of breaking down blood clots. The activity of an enzyme that promotes fibrin breakdown and is responsible for tissue remodeling, in the setting of wound healing, can be inhibited by the protein PAI1 (Kumari *et al.*, 2024; Mujwar, 2021b; Mujwar & Pardasani, 2022; Sharma *et al.*, 2020). PAI1-targeting therapy has the potential to promote wound healing by increasing fibrinolysis and assisting tissue regeneration. Many studies reveal that PAI-1 inhibitors are efficient at accelerating wound healing in animal models. Clinical studies are being conducted in humans to test the safety and effectiveness of these inhibitors. Furthermore, PAI-1 inhibitors have shown immensely positive results in treating conditions other than wound healing, such as thrombotic disorders, cardiovascular diseases, and cancer (Gupta *et al.*, 2022a; Hsieh *et al.*, 2019; Shah *et al.*, 2019).

Computational techniques for drug design and discovery are used as they provide benefits such as speed, cost-effectiveness, and accuracy in generating viable drug candidates with particular target selectivity and potency. These techniques are used as they can lessen the reliance on animal testing, ultimately resulting in lower costs and fast and better development of newer medications (Er-rajy *et al.*, 2023b; Kciuk *et al.*, 2022b; Kciuk *et al.*, 2023; Shah & Mujwar, 2022; Sharma *et al.*, 2023). The goal of this study was to identify the most effective active ingredient obtained from plants that contribute to wound healing abilities. Furthermore, we were able to identify the most plausible method by which this active ingredient functions.

2. Experimental

2.1. Ligand Library Preparation

A molecular ligand library of more than 85 ligands derived by considering diverse plant sources was prepared by referring to a wide range of available literature. These plants have an extensive historical record of being used for the management of wounds and associated conditions since ancient times. The concerned plants are selected for the generation of a ligand library based upon their already reported therapeutic potential for the treatment of complex wounds and related disorders. Therefore, it has been expected that the broad range of ligands derived from the above-mentioned plant sources can significantly contribute to the discovery of a potent wound-healing agent and will reveal the involved physiological mechanisms for the generation of their therapeutic effect (Er-rajy *et al.*, 2023a; Er-rajy *et al.*, 2023c; Gielecińska *et al.*, 2023; Kciuk *et al.*, 2022a, Kciuk *et al.*, 2022c; Mujwar *et al.*, 2021).

2.2. Macromolecular Target Selection and Preparation

Plasminogen activator inhibitor-1, or PAI1, inhibits tissue plasminogen activation (tPA) by preventing serine protease from doing its job, which causes tissues linked to wounds to recover more slowly. One protein that is essential for controlling the wound-healing process is PAI1. The main function of this protein is to regulate the activity of plasminogen activators, which are enzymes that break up blood clots and promote tissue healing (Jang *et al.*, 2021; Sarnik *et al.*, 2021). Therefore, PAI1 is an important target for wound care, and we are currently searching for new plant-based PAI1 inhibitors that may be applied to the

management of complicated wounds (Donati *et al.*, 2018; Shi *et al.*, 2022; Ahmed *et al.*, 2023; Malik *et al.*, 2023; Mittal *et al.*, 2023). A three-dimensional model of the PAI1 complexed with an antagonist AZ3976 (PDB ID: 4AQH) was procured from the RCSB PDB database (Berman *et al.*, 2002; Fjellström *et al.*, 2013). To generate nascent receptor and ligand molecules for docking studies, the structural model of PAI1 and its complexed reference ligand was stripped by removing each one in turn.

2.3. Molecular Docking Studies

Use the AutoDock Tools version 4.2 in order to re-dock this newly created receptor with the PAI1 reference ligand (Chauhan *et al.*, 2021; Gupta *et al.*, 2022b; Kciuk *et al.*, 2024; Morris *et al.*, 2009). The grid box has been prepared by considering the extended conformations of the bioactive crystallized reference ligand as well as the interacting residues for the same. Docking parameters are validated using reference ligand conformation and the chemical similarity with respect to its active region. The created herb-based molecular library is virtually screened against the PAI1 receptor by the approach that has proven itself (Kaur *et al.*, 2016; Rani *et al.*, 2022; Rani & Goyal, 2019). The validated grid parameters considered in the current study for the execution of docking analysis against the human PAI1 receptor were tabulated in Table 1.

Table 1: Grid Parameters Considered in the Current Docking Analysis of Human PAI1 Receptor.

S. no.	Target	x-dimension	y-dimension	z-dimension	Spacing (Å)	x center	y center	z center
1	PAI1	40	40	40	0.386	-28.102	2.09	1.213

2.4. Molecular Dynamics Simulation

The compound, emodin, was selected for MD simulation based on its chemical interaction with the target PAI1 receptor and its docking score. Emodin, a derivative of anthraquinone, is also a naturally available compound found in Rheum palmatum, Polygonum cuspidatum, and Aloevera. This compound possesses the most widespread spectrum of therapeutic effects. Emodin, through interfering with NF-κB and MAPK pathways, exerts its potent anti-inflammatory effect by suppressing the expression of TNF-α, IL-6, and IL-1β, which are pro-inflammatory cytokines. It also suppresses the expression of COX-2 and iNOS, which further mitigates the inflammation. It also exerts considerable anticancer activity, which includes inducing apoptosis through both mitochondrial and death receptor pathways. Tumor proliferation is inhibited via the PI3K/Akt, Wnt/β-catenin, and JAK/STAT3 pathways, whereas metastasis is prevented by the downregulation of MMPs and EMT markers. Emotion's antioxidant results are due to ROS scavenging as well as the promotion of the cellular antioxidant enzymes SOD, CAT, and GPx, where these enzymes help in detoxifying the cell from oxidative stress-induced damage. In addition, it is observed to exhibit antimicrobial activity against Staphylococcus aureus, Escherichia coli, and Helicobacter pylori, in addition to antiviral activity against hepatitis B, influenza, and SARS-CoV-2 through repression of viral replication. Emodin has been reported to enhance neuronal survival by reducing neuroinflammation and oxidative stress, thus making it a potential therapeutic candidate for neurodegenerative disorders such as Alzheimer's and Parkinson's disease by modulating amyloid-beta and α-synuclein aggregation. These diverse pharmacological effects highlight emodin's potential as a promising therapeutic agent in various pathological conditions. MD simulation was performed on the macromolecular complex of PAI1 with complexed emodin for 100 ns using the Desmond module of Schrodinger's Maestro program (Bowers *et al.*, 2006; Bowers *et al.*, 2007; Dhankhar *et al.*, 2023; Dhankhar *et al.*, 2024b; Kumar *et al.*, 2022; Li *et al.*, 2023). After adding special solvent molecules, appropriate ions are added to balance them. To remove any kind of steric conflicts or weak atom-to-atom interactions, the system was relaxed, and the steepest descent method was followed to reduce the energy of the system. Equilibrium was introduced in the system by using the short series simulations with low temperature with constant pressure (NPT). In addition to a slow increase in temperature, the system is subjected to positional restrictions as well (Shah & Mujwar, n.d.). This presents the possibility of the system already being in an equilibrated, stable condition before the simulation. For correct results, it is simulated for 100 ns, keeping atom positions, energies of the systems, and the values of RMSD in consideration, hence making it relatively easier to understand how the complex behaves dynamically, as well as providing long-term information regarding its structure and the functionality stability (Er-rajy *et al.*, 2023e, Er-rajy *et al.*, 2023d; Gupta *et al.*, 2023; Kciuk *et al.*, 2022b; Shah *et al.*, 2020; Shinu *et al.*, 2022).

3. Results

3.1. Design of Ligand Library

A library of ligands from herbs was derived by considering 85 ligands from the mentioned chemical classes. All of the

ligands that were taken into consideration for the ligand library had their names, chemical structures, and biological sources listed in Table S1 as supplemental material. Each ligand's two-dimensional structure was created using ChemDraw 9.0 software using its isomeric SMILES, which were obtained from the PubChem database. Their three-dimensional structure was then generated for computational screening against the target linked to wound pathogenesis by minimizing their energy using the MMP forcefield of the Chem3D tool.

3.2. Target Selection

X-ray diffraction (XRD) at a resolution of 2.40 Å was used to determine the crystallized model of the human PAI1 receptor obtained from the RCSB PDB library. The 383 amino acids that make up the trimeric chain of the PAI1 receptor are deleted to leave behind a monomeric chain (Adasme *et al.*, 2021; Berman *et al.*, 2000; Berman *et al.*, 2002; Chauhan *et al.*, 2023; Dhankhar *et al.*, 2024a; Dhankhar *et al.*, 2024c; Ghosh *et al.*, 2022). To obtain the nascent receptor needed for the docking investigation, the bound ligands were removed from the monomeric chain.

3.3. Molecular Docking Studies

The utilized docking protocols in the current study were validated by redocking the separated structures of the PAI1 receptor with the reference ligand (AZ3976). The currently used docking parameters, including grid parameters, were successfully validated as the resulting binding score for the reference ligand was observed within the range of -5 to -15 kcal/mol, claiming the reference ligand is showing reversible binding with adequate strength within the macromolecular active site. Additionally, it has been shown that the reference ligand's docked conformation exhibits a chemical interaction with the target PAI1 receptor that is exactly the same as that which was present in its bioactive macromolecular complex with an observed RMSD value of 0.27 Å, indicating that the binding occurs in the same way as it does in the human body. The exact overlaid docked conformation of the reference ligand over its bioactive conformation is depicted in Figure 1. Ultimately, based on the observed validation results, it has been determined that the docking methodology under consideration is mimicking the complexation process between the reference ligand and the PAI1 receptor that occurs in the human body. Using the verified docking parameters, a previously prepared herbal-based ligand library was tested against the PAI1 receptor. Based on the minimum binding score and the greatest binding interactions seen with the macromolecular target, the lead compounds were shortlisted following the completion of the virtual screening. Table 2 showed the shortlisted leads observed binding score and interacting macromolecular residues against the PAI1 receptor.

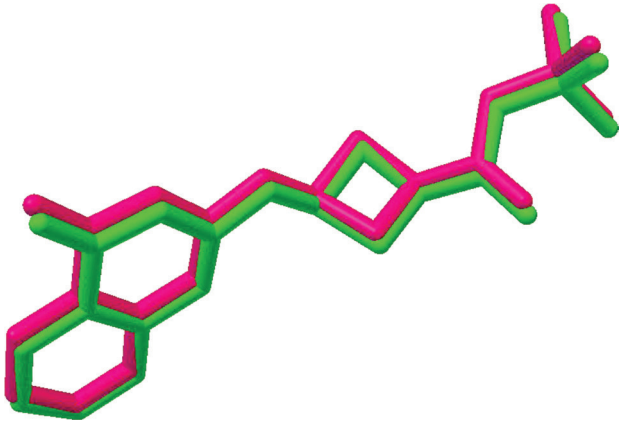
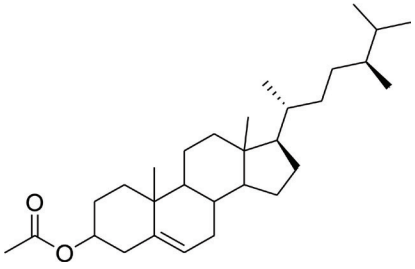
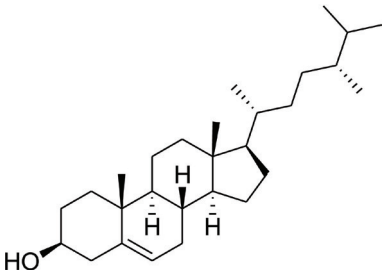
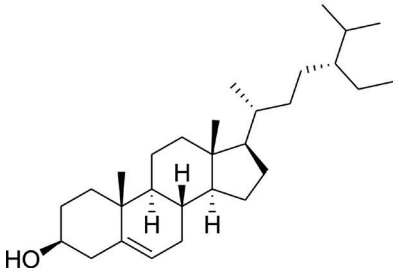
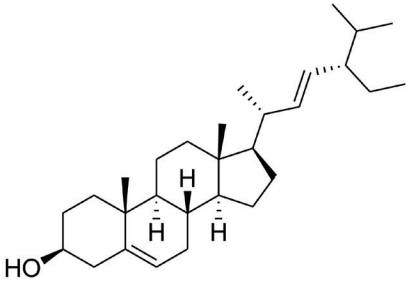
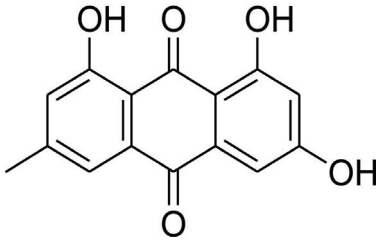
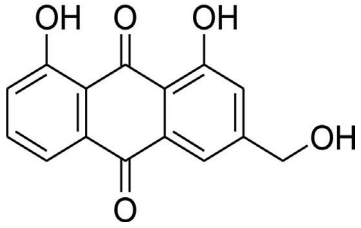
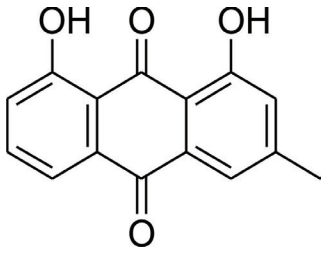
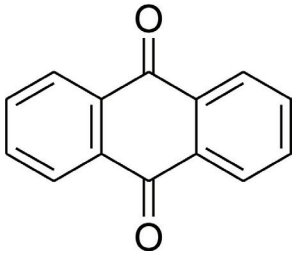
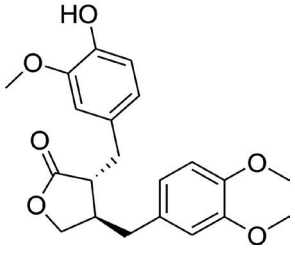
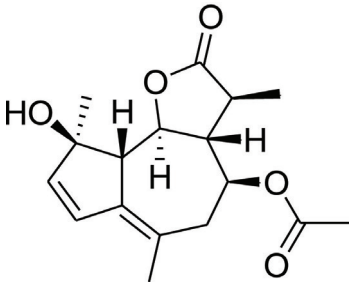
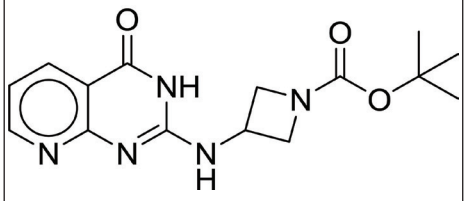


Figure 1: Overlay: Overlaid Docked Conformation of the Reference Ligand over its Bioactive Conformation

Table 2: Binding Score and Interacting Residues for the Shortlisted Leads against PAI1 Receptor

S. No.	Compounds	Structure	Docking Score	Interacting Residues		
				van der Waals	H-bond	Alkyl
1	Ergost-5-en-3-ol acetate		-11.44	Ser-41 Thr-94 Tyr-37	Asp-95	Ala-12 Ala-40 Ala-44 Phe-64 Ile-66 Leu-75 Tyr-79 Phe-117 Arg-118

2	Campesterol		-10.97	Ser-41 Thr-93 Phe-64 Asp-95		Ala-12 Tyr-37 Ala-40 Ala-44 Leu-75 Leu-78 Tyr-79 Phe-117 Arg-118
3	Beta-Sitosterol		-10.62	Ser-41 Phe-64 Thr-94 Asp-95		Tyr-37 Ala-12 Tyr-37 Ala-40 Ala-44 Leu-75 Leu-78 Tyr-79 Phe-117 Arg-118
4	Stigmasterol		-10.50	Arg-76 Thr-93 Phe-64 Ile-66	Ala-40	Ala-12 Tyr-37 Ala-44 Leu-75 Leu-78 Phe-117 Arg-118
5	Emodin		-9.27	Tyr-79 Thr-94	Tyr-37 Ser-41 Leu-75 Arg-76 Thr-93 Asp-95 Leu-116	Phe-117
6	Aloe Emodin		-8.91	Tyr-79 Thr-94 Arg-118	Tyr-37 Ser-41 Leu-75 Arg-76 Thr-93 Leu-116	Ala-44 Phe-117
7	Chrysophanol		-8.85	Ser-41 Thr-94	Tyr-37 Arg-76 Thr-93 Leu-116	Leu-75 Tyr-79 Phe-117

8	Anthraquinone		-8.28	Tyr-79 Thr-94	Tyr-37 Ser-41 Arg-76 Thr-93	Leu-75 Phe-117
9	Arctigenin		-8.26	Ser-41 Arg-76 Thr-94		Ala-12 Tyr-37 Ala-44 Leu-75 Leu-78
10	Matricin		-8.23	Ser-41 Phe-117 Thr-93 Thr-94 Asp-95	Arg-76 Leu-75	Tyr-37
11	TB7 (Reference)		-8.35	Ser-41 Thr-94	Arg-76 Asp-95	Ala-12 Tyr-37 Ala-40 Ala-44 Phe-64 Ile-66 Leu-75 Leu-78 Arg-118

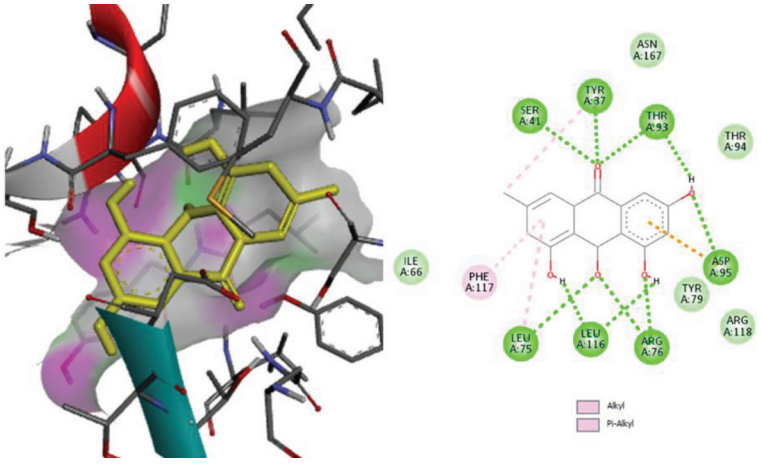


Figure 2: Binding Interactions: Two-Dimensional Binding Interactions and Three-Dimensional Binding Conformation of the Emodin with the Human PAI1 Receptor

The provided image illustrates molecular docking interactions between a ligand (highlighted in yellow) and a protein binding site, revealing key interactions that contribute to ligand stability and affinity. In the left panel, the ligand is nestled within the binding pocket, which is represented by a gray surface, indicating its spatial fit within the receptor. Structural elements of the protein, including α-helices (red) and β-sheets (cyan), provide a contextual framework for understanding the binding environment. The presence of purple and pink surface regions signifies alkyl and π-alkyl interactions, which contribute to hydrophobic stabilization of the ligand. In the right panel, a 2D interaction map provides a more detailed breakdown of the binding forces. Green dotted lines represent hydrogen bonds, which play a crucial role in ligand specificity and stability by forming strong polar interactions with key amino acid residues. Pink dashed lines indicate alkyl and π-alkyl interactions, where hydrophobic contacts with residues such as leucine and phenylalanine enhance ligand retention in the pocket. Additionally, the presence of an orange dashed line suggests a π-cation or π-anion interaction, an electrostatic force that strengthens the ligand's binding affinity. The labeled amino acid residues (within green circles) further highlight the specific binding interactions involved.

3.4. MD Simulation

The human PAI1 receptor complexes with emodin were chosen for MD simulation in order to assess their thermodynamic stability over a 100 ns time period. The final molecule was shortlisted to perform MD simulation based upon its highest binding affinity and observed chemical interactions for the concerned target receptor. To carry out the therapeutic response, the drug-receptor combination must be stable enough across a nanoscale time range. Consequently, Schrodinger's Desmond program version 2022.4 was used to perform a 100 ns MD simulation on the macromolecular complex. The 383 amino acids that make up the monomeric chain of the target PAI1 receptor have 3037 heavy atoms out of a total of 6066 atoms. To assess their thermodynamic stability, structural changes, and RMSD analysis of the macromolecular backbone were carried out during the 100 ns simulation. Three flexible bonds made up of twenty heavy atoms totaling thirty atoms make up the complexed ligand emodin. Throughout the simulation, the human PAI1 receptor-emodin conjugate has shown excellent stability. While the bound ligand emodin showed slight variations in its RMSD value in the receptor cavity, ranging from 2.0 to 4.0 Å, the RMSD value of the receptor's backbone was observed to fluctuate between 1.4 and 2.4 Å. The discovered RMSD of the human PAI1 complex with emodin is shown in Figure 3.

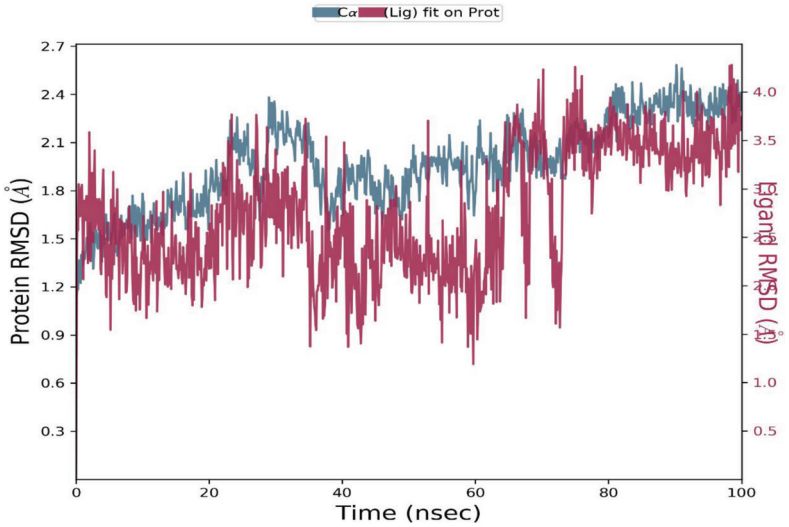


Figure 3: RMSD for the Cα Chain of the PAI1 Complexed with the Ligand Emodin Detected while Executing a 100 Ns MD Simulation

The RMSF value of a protein or ligand structure can be used to quantify the degree to which the atoms have shifted from their original positions. It is a crucial metric for figuring out the macromolecular complex's flexibility and dynamic behavior. Protein RMSF is significant because, by revealing the relative flexibility of different areas, it may be used to assess stability and forecast protein dynamics. According to an MD-based assessment of the human PAI1 receptor complexed with emodin, the RMSF for the ligand emodin ranged from 0.8 to 1.1°C, while the RMSF for the Cα backbone was determined to be between 0.5 and 2.0°C.

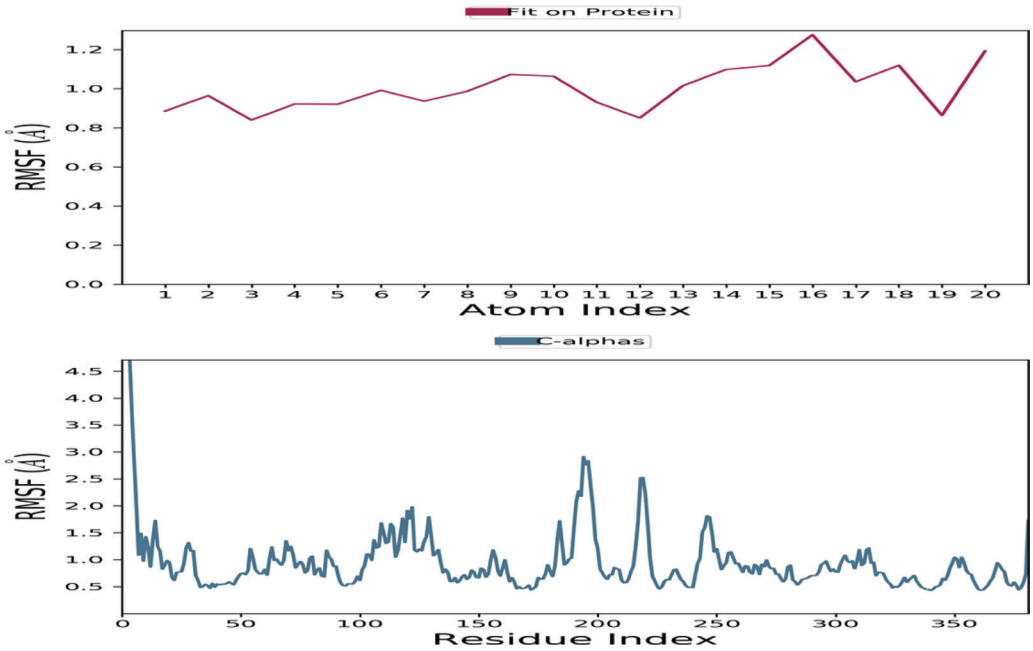


Figure 4: Root Mean Square Fluctuation: Observed RMSF for PAI1 Complexed with Ligand Emodin Detected while Executing 100 Ns MD Simulation

The human PAI1 receptor's interaction residues with the ligand emodin are depicted in Figure 5.

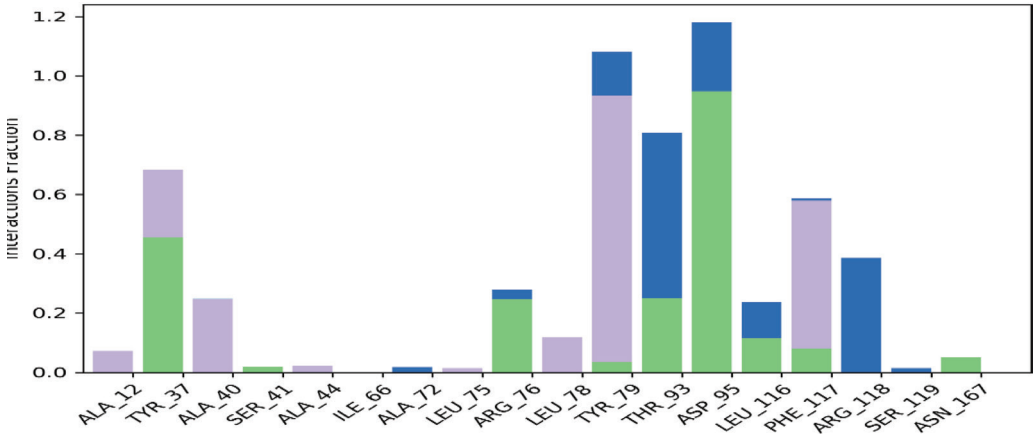


Figure 5: Protein-Ligand Contacts: Protein-Ligand Interactions Identified between the Human PAI1 Receptor and Ligand Emodin

The interactions were visualized using different colored bars, with green representing hydrogen bonds, blue representing water bridges, and purple representing hydrophobic interactions.

The bar chart represents the interaction fractions of various amino acid residues with a ligand during a molecular dynamics simulation. Each colored segment in the bars corresponds to different types of molecular interactions contributing to ligand binding stability. The green segments indicate hydrogen bonding interactions, which play a crucial role in ligand specificity and stability by forming directional, polar interactions with specific residues. The purple segments represent hydrophobic interactions, which involve nonpolar contacts between the ligand and residues such as tyrosine, phenylalanine, and leucine, enhancing ligand retention in the binding pocket through van der Waals forces. The blue segments correspond to electrostatic interactions, including salt bridges and charge-based attractions between positively and negatively charged residues, which strengthen the binding affinity of the ligand. The x-axis lists the amino acid residues involved in ligand interactions, while the y-axis represents the interaction fraction, indicating

the proportion of the simulation time during which each interaction is maintained. Higher bars suggest stronger and more persistent interactions. The presence of multiple interaction types for a single residue suggests a key role in stabilizing the ligand within the binding site. Understanding these interaction distributions helps assess the binding efficiency and potential pharmacological relevance of the ligand-protein complex. The simulation revealed that the ligand emodin interacted with the human PAI1 receptor by forming hydrophobic bonds with the amino acids Tyr37, Arg76, Asp95, Leu116, and Asn167 through hydrogen bonds, while amino acids Thr93 and Arg118 interacted through water bridges.

4. Discussion

This present study explores the possibility of using plant-derived compounds as a lead for targeting the epigenetic regulator PAI-1 in wound progression. The computational screening of a library of plant-based ligands that identified emodin as a promising inhibitor offers an exciting step toward developing novel therapeutics for wound management. The results from the molecular docking along with the results from the MD simulation validate emodin as an effective ligand for PAI-1; they give more insight into mechanisms of inhibition, as well as the structural stabilities of this ligand and receptor complex. PAI-1 inhibitors have been the subject of several studies, as well as small-molecule inhibitors and peptides, aimed at modulating its activity in pathological conditions such as fibrosis and cancer. Compounds such as tiplaxtinin and baicalin have been studied for their ability to inhibit PAI-1, but many of these molecules are yet to demonstrate clinical efficacy or sufficient bioavailability. The inhibitory effect of emodin is consistent with prior reports, where flavonoids and anthraquinones were identified as potential inhibitors of PAI-1 activity. This characteristic suggests that emodin might share common mechanistic pathways with other known compounds. The chemical structure of emodin, particularly its anthraquinone backbone, may offer a separate advantage over other flavonoid-based inhibitors in terms of specificity and potency. Translational prospects for emodin as a therapeutic agent are promising but remain speculative at this stage. The findings indicate that emodin is capable of binding to the PAI-1 receptor with high affinity, suggesting its potential for therapeutic use in wound healing. However, before emodin can be considered for clinical use, in vitro and in vivo validation are essential to confirm its efficacy in more biologically relevant systems. The in vitro studies by cultured cells and subsequent animal models of wound healing would be needed to establish the pharmacodynamics, bioavailability, and safety profile. The absence of these experimental validations in the current study is a key limitation that must be addressed in future work. Second, although molecular dynamics simulations can give insights into the stability and binding interactions of emodin with PAI-1, those simulations also cannot assume to be at the level of complexity that occurs inside a living organism. For that reason, the actual behavior of emodin in the biological environment, such as pharmacokinetics, distribution, and metabolism, is completely unknown. This will, therefore, have immense importance for ascertaining the feasibility of emodin as a therapeutic agent. This study primarily focuses on computational methods, and while the results are promising, they are not conclusive. The lack of experimental validation is a significant limitation that should be addressed in subsequent studies. Additionally, the computational model used in docking may not account for all the biological variables present in a living organism. The other challenge was that no structural information of the PAI-1 ligand-binding domain in complex with a full range of cofactors available might affect the accuracy of docking predictions.

5. Conclusion

Finally, the molecular interaction between emodin and PAI-1 receptor docking analysis has been investigated. According to the results obtained, emodin has a high binding affinity for PAI-1 and is capable of efficiently inhibiting its activity. The study examines inhibition of PAI-1 in the setting of wound healing but lacks discussion regarding clinical implications of this strategy. PAI-1 is critical in wound healing through regulation of fibrinolysis, extracellular matrix remodeling, and cell migration; however, dysregulation of PAI-1, most importantly overexpression, is associated with impeded healing and chronic wound formation. High levels of PAI-1 lead to excessive fibrin deposition, decreased plasmin activity, and impaired tissue remodeling, thus resulting in fibrosis and delayed re-epithelialization. To strengthen the study, a more comprehensive discussion on the regulatory mechanisms of PAI-1 in chronic wounds is needed, including how its imbalance worsens wound pathophysiology. Computational analysis is a useful method for drug research and discovery since it makes it possible to efficiently and accurately identify and optimize possible therapeutic candidates. So, the conducted study provided a new aspect of emodin's action mechanism and brought the focus on this compound as an interesting candidate drug for wound healing therapy. As an outcome of such a study, any future experimental study aimed at confirmation of the emodin in preclinical or clinical stages on safety and efficiency as a drug for wound healing can be undertaken. Generally, such research helps make innovative treatments possible for wound healing, which stands as a paramount global health issue. By exploring the

potential of natural compounds, such as emodin, as sources of new drugs, this research offers a promising approach for the development of effective and safe wound healing therapies. Moreover, exploration of plant-derived compounds as potential PAI-1 inhibitors would also add value to the translational aspect of the study. Most phytochemicals exhibited an ability to modulate the expression of PAI-1. Therefore, PAI-1 inhibition remains a promising approach in the field of restoring the balance of fibrinolysis, fibrosis, and further tissue regeneration. It is expanded here, however, for greater comprehensive understanding and realization of PAI-1 inhibition and clinical applications in wound healing. Further studies are required to investigate the translational potential of emodin as a drug candidate for clinical use.

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Authorship Contribution

Ankita Sharma performed the docking and dynamic study. Mohammed Er-rajy analyzed the data and wrote the initial manuscript draft. Mohammad Elfadili have supervised the whole study and reviewed the final manuscript draft. Ozkan Fidan helped in the preparation of the final manuscript draft.

Conflict of Interest

The authors have no competing conflict of interest to declare.

Declaration

It is an original article and has neither been sent elsewhere nor published anywhere.

Ethical Approvals

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