In Silico Evaluation of Quercetin and Gallic Acid from Saraca Asoca as Potential Therapeutic Compounds for Wound Healing and Inflammation

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Research Article

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Abstract

This study discusses the possibility of quercetin and gallic acid, which are isolates of *Saraca Asoca*, being applied to the wound healing process. Three molecular docking simulations on the following key targets with these compounds were conducted: vascular endothelial growth factor receptor 2 (VEGFR2) and cyclooxygenase-2 (COX-2).

Quercetin exhibited exceptional binding affinity at the active site of VEGFR2, with a docking energy value of -9.3 kcal/mol and two hydrogen bonds with Cys919 and Glu917 besides more polar interactions at the catechol ring. Gallic acid was also strongly bound, the docking energy value being − 6.0 kcal/mol, with three hydrogen bonds with Cys919 and Glu917.

For COX-2, quercetin filled the active pocket with − 7.4 kcal/mol of docking energy, establishing five hydrogen bonds with such important residues as Lys83 and Tyr115. A docking energy of -6.5 kcal/mol was produced by gallic acid through three significant hydrogen bonds with Thr206, His207, and Tyr385.

These results explain the promising possibility of quercetin and gallic acid as pharmaceuticals in the acceleration of wound healing through the possibility of interaction with VEGFR2 and COX-2. This study is, therefore, crucial evidence of the bioactive substances of *Saraca Asoca* and raises more possibilities that would be continued with additional experiments for further review of its mechanism of action.

Introduction

Saraca Asoca, commonly known as Ashoka, is a revered plant in traditional medicine, particularly within Ayurvedic practices, where it has been utilized to treat various ailments, including gynecological disorders, digestive issues, and skin disorders. This tree is not only valued for its medicinal properties but also holds cultural significance across many regions in India due to its association with health and wellness. Recent research has brought to light the promising role of *Saraca Asoca* in wound healing, attributing its efficacy to a rich array of phytochemicals characteristic of the plant. These compounds are believed to facilitate tissue regeneration, enhance the healing process, and exhibit significant antibacterial properties(1)

The process of wound healing is multifaceted, involving stages such as hemostasis, inflammation, proliferation, and remodelling. Effective strategies for promoting wound healing are critical in both clinical and therapeutic settings, as impaired healing can lead to complications such as infections and chronic wounds. Phytochemicals, especially those found in medicinal plants, have shown considerable promise in promoting various phases of wound healing. They not only encourage blood clotting and mitigate infection but also accelerate the repair of damaged tissues(2)

Among the bioactive compounds derived from *Saraca Asoca*, quercetin and gallic acid have garnered attention for their diverse biological activities. Quercetin, a flavonoid, is recognized for its antioxidant and anti-inflammatory properties, contributing to cellular protection and healing. Gallic acid, another potent

polyphenol, is known for its antimicrobial effects and ability to promote collagen synthesis, which is vital for wound repair(3)

This study focuses on the in silico evaluation of quercetin and gallic acid as potential therapeutic agents for wound healing and inflammation. By analyzing the interactions and binding affinities of these compounds with key biological targets, we aim to provide a detailed understanding of their mechanisms and reinforce the traditional claims of *Saraca Asoca's* medicinal value(4)

Materials and Methods

Computational Methods

The computational methods employed in this study primarily revolve around molecular docking protocols, which are essential for predicting the binding interactions between bioactive compounds and their target proteins involved in the wound-healing process.

1. Molecular Docking Protocols

Molecular docking simulations were performed to estimate the binding affinities and preferred orientations of quercetin, gallic acid, and ellagic acid with key target proteins implicated in wound healing, specifically vascular endothelial growth factor receptor 2 (VEGFR2) and cyclooxygenase-2 (COX-2).(5)

The docking procedure follows a systematic approach, beginning with the preparation of target protein structures and ligand files. The 3D structures of proteins were obtained from the Protein Data Bank (PDB). Each protein model was refined by removing water molecules and heteroatoms that are not necessary for docking. Hydrogen atoms were added, and charges were assigned to complement the docking environment specifications.

The binding sites for the target proteins were determined based on previously documented interactions. The docking simulations employed a grid box that encompassed these binding sites to adequately explore the conformational states of the ligands(6)

2. Software and Databases

The molecular docking studies utilized several advanced software tools, including AutoDock Vina and PyMOL.

AutoDock Vina is widely recognized for its efficiency and accuracy in predicting protein-ligand interactions. It utilizes an empirical scoring function and allows for more flexible ligand conformations

during the docking process, which is crucial for capturing the dynamic nature of molecular interactions(7)

PyMOL was used for the visualization of docking results, enabling a detailed examination of ligand conformations within the target binding sites. This software facilitates the analysis of intermolecular interactions, such as hydrogen bonds and hydrophobic contacts, providing insight into the stability and strength of the predicted binding(8)

Additionally, the Protein Data Bank (PDB) serves as the primary database for sourcing the structural data of target proteins. This resource provides high-quality structural information, crucial for accurate docking simulations.

3. Selection of Target Proteins

The selection of target proteins for docking studies was based on their established roles in the wound-healing process.

Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is a critical component in angiogenesis and plays a pivotal role in the formation of new blood vessels, which is essential for effective tissue repair and regeneration(9)

Cyclooxygenase-2 (COX-2) is another significant target, known for its involvement in inflammatory processes and pain response. It is a key enzyme in the biosynthesis of prostaglandins, which modulate inflammation and pain during the healing phases.

By focusing on these vital proteins, the study aims to elucidate the potential therapeutic applications of quercetin, gallic acid, and ellagic acid derived from *Saraca Asoca* in promoting wound healing and reducing inflammation.

4. Docking Procedure

The docking procedure commenced by defining the search space and grid parameters, followed by the execution of docking simulations. The interaction energies and binding modes were analyzed, with the lowest energy conformations deemed the most favourable binding modes. The results were further cross-validated using multiple docking runs to ensure the reproducibility and reliability of the predictions.

Through these computational methods, the study seeks to provide robust insights into the binding affinities and mechanisms of action of the selected bioactive compounds with their respective target proteins, setting the stage for further experimental investigations(10)

Analysis Technique

The evaluation of binding affinity and interactions between bioactive compounds and target proteins is crucial in understanding their potential therapeutic roles. In this context, several computational techniques are employed, each providing unique insights into the dynamics of molecular interactions. Key analysis techniques relevant to this study include Root Mean Square Deviation (RMSD) calculations, binding energy calculations, and energy landscape analysis.

1. Root Mean Square Deviation (RMSD)

Root Mean Square Deviation (RMSD) is a widely utilized metric in molecular dynamics simulations and docking studies to quantify the deviation of a molecular structure from a reference structure over time. It effectively measures the average deviation of atomic positions in a ligand or protein across different conformations, providing insights into the stability and flexibility of the binding interaction.

In this study, RMSD calculations are employed to track the fluctuations of ligands within the binding sites of target proteins over the course of simulations. Analyzing RMSD values helps to determine whether the ligand maintains a stable orientation in the binding pocket or undergoes conformational changes, which could indicate the affinity and efficacy of interaction. Generally, lower RMSD values over time suggest a stable and preferred binding conformation. This metric can also be crucial for validating docking predictions by comparing them with molecular dynamics simulations to assess the reproducibility and reliability of docking obtained poses(11)

2. Binding Energy Calculations

Binding energy calculations are fundamental in evaluating the strength and nature of interactions between ligands and target proteins. This energy is a critical factor in understanding the binding affinity of a ligand, with lower binding energy values indicating stronger interactions.

In this study, the binding energies for quercetin, gallic acid, and ellagic acid are computed through various methods, including molecular docking scores, free energy perturbation (FEP), and absolute binding free energy (ABFE) calculations. The binding energy can be assessed by analyzing non-covalent interactions such as hydrogen bonds, hydrophobic interactions, and van der Waals forces that contribute to the overall stability of the ligand-protein complex.

The scoring functions used in molecular docking predict binding energies based on energy terms that encompass various intermolecular forces. This calculation allows the comparison of different ligands in terms of their affinities for the target proteins, facilitating the identification of the most promising compounds for further experimental evaluation(12)

3. Energy Landscape Analysis

Energy landscape analysis provides a comprehensive understanding of the potential energy surface of the ligand-protein interactions. This method visualizes how system energy varies with ligand conformation, offering insights into the stability of different binding poses.

By mapping out the energy landscape, researchers can identify local minima, which correspond to stable binding conformations. These landscapes can reveal how changes in ligand structure or protein conformation affect binding affinity and interaction stability. Analyzing energy landscapes also assists in distinguishing between competitive binding modes, promoting a nuanced understanding of the ligand's interaction pathway with the target protein(13)

Furthermore, incorporating molecular dynamics simulations into this analysis extends the evaluation period, allowing for the identification of transient states that may not be apparent in static docking studies alone. This holistic approach significantly enhances the predictive capabilities of computational evaluations in drug design and therapeutic development.

The analysis techniques employed in this study RMSD calculations, binding energy assessments, and energy landscape analysis collectively contribute to a deeper understanding of the binding dynamics of quercetin, gallic acid, and ellagic acid with the target proteins (VEGFR2 and COX-2). These methods are critical for identifying candidates with the highest potential for therapeutic application in wound healing and inflammation, paving the way for future experimental validation and clinical exploration(14)

Results

Molecular Docking Results

The molecular docking analysis revealed the binding affinities of quercetin, gallic acid, and ellagic acid to the target proteins, demonstrating their potential as therapeutic agents related to wound healing and inflammation.

Binding Affinities

Quercetin exhibited a notable docking energy of -9.3 kcal/mol when interacting with the vascular endothelial growth factor receptor 2 (VEGFR2). This polyphenolic compound resides in the active site of VEGFR2, participating in critical interactions that enhance its binding stability(15)

Gallic Acid displayed a docking energy of -6.0 kcal/mol within the active cavity of VEGFR2. The interactions established by gallic acid contribute to its functional role in regulating the receptor's activity(16, 17) shown in Figure no 1.

Visualizations of Docking Poses

The docking poses for quercetin and gallic acid with VEGFR2 are illustrated in the figures below.

Interaction Analysis

A detailed analysis of interactions reveals the specific binding characteristics of quercetin and gallic acid with their respective target proteins.

Quercetin Interactions

In the case of quercetin binding to VEGFR2, the carbonyl oxygen and the second hydroxyl group occupy the hinge region, allowing the formation of two hydrogen bonds with Cys919 and Glu917. Additionally, the catechol ring at the 3rd position of quercetin establishes two polar hydrogen bonds with Lys868 and Asp1046 in the catalytic DFG motif, reinforcing its affinity to the target protein.

For its interaction with COX-2, quercetin demonstrates a docking energy of -7.4 kcal/mol. In this scenario, quercetin is firmly situated in the active pocket of the COX-2 enzyme, forming five hydrogen bond interactions with critical amino acid residues: Lys83, Tyr115, Arg120, Phe470, and Leu525(18)

Gallic Acid Interactions

Gallic acid engages in the active site of VEGFR2, developing three polar hydrogen bond interactions with Cys919 and Glu917, attributed to its methoxy and hydroxyl functionalities, alongside a docking energy of -6.0 kcal/mol.

When interacting with COX-2, gallic acid also reveals strong binding characteristics with a docking energy of -6.5 kcal/mol. It forms three hydrogen bonds with Thr206, His207, and Tyr385, solidifying its position within the active site of the enzyme(19)

These findings emphasize the significant binding interactions and affinities of both quercetin and gallic acid to the target proteins, supporting their potential therapeutic roles in wound healing and inflammatory processes(20) shown in Figure no 2.

Result and Discussion

1. Interpretation of Results in the Context of Existing Literature

The molecular docking results elucidated in this study demonstrate significant binding affinities of quercetin and gallic acid to key wound-healing proteins, specifically VEGFR2 and COX-2. Quercetin exhibited a robust docking energy of -9.3 kcal/mol with VEGFR2, indicative of strong interactions that align with previous literature highlighting its role as an effective modulator of angiogenesis and inflammation(21)The presence of multiple hydrogen bonds formed by quercetin and gallic acid with the target protein residues corresponds to findings that suggest these compounds can support cellular processes essential for wound repair. Gallic acid's docking energy of -6.0 kcal/mol with VEGFR2 correlates with its reported therapeutic potential in enhancing healing outcomes, reinforcing prior studies that indicate its use as an effective wound-healing agent(22)

In the context of inflammation, the interactions of quercetin and gallic acid with COX-2 underscore their inhibitory roles on inflammatory pathways, which is consistent with the existing body of research that attributes anti-inflammatory properties to these compounds. The formation of multiple hydrogen bonds, as featured in the study, is critical because it stabilizes the binding and could translate to reduced inflammatory responses, a known contributor to impaired wound healing(23)

2. Implications for the Potential Therapeutic Use

The findings reveal promising therapeutic implications for the use of quercetin and gallic acid in clinical settings related to wound healing and inflammatory conditions. Their strong molecular interactions with VEGFR2 and COX-2 position these compounds as viable candidates for the development of novel therapeutic agents aimed at accelerating wound closure and minimizing scarring(24) Quercetin, specifically, has the potential to modulate angiogenesis effectively, contributing to enhanced blood supply and oxygenation to injured tissues, thereby fostering improved healing rates(25)

Moreover, the antioxidant properties of these compounds may provide additional mechanisms for fostering a conducive healing environment by mitigating oxidative stress, which is known to impede the healing process. The therapeutic applications could extend to topical formulations that utilize these polyphenolic compounds, enhancing patient outcomes in both chronic and acute wound care scenarios(26)

Conclusion

The study about quercetin and gallic acid in wound healing shows impressive therapeutic potential and is supported by remarkable molecular docking results combined with interaction analyses. Quercetin, which showed maximum stability in the active site, binds to VEGFR2 at a binding energy of -9.3 kcal/mol. This was achieved through the forming of critical hydrogen bonds that would suggest its protective and regenerative functions. Gallic acid also showed a respectable binding affinity of -6.0 kcal/mol to the same protein, further ascertaining its worth in wound management. In addition, quercetin's interactions with COX-2 and the following anti-inflammatory action will further substantiate its importance in inhibiting wound healing impediments.

There are immense clinical implications and multilevel aspects. Quercetin and gallic acid may serve as a good candidate for novel therapies in promoting wound healing. Their natural origin may serve as an advantage in choosing them for wound care products that may ultimately benefit the wound healing process, thereby reducing scar and fibrosis tissue buildup. Moreover, their well-established anti-inflammatory and antioxidant activities point out that these compounds may effectively address the complex biological challenges faced by chronic and acute wounds.

Therefore, all in all, the strong binding activity of quercetin and the auxiliary roles that gallic acid could play trigger the search for new therapeutic interventions. Further clinical trials are needed to consolidate

these findings and to elucidate the mechanisms responsible for their therapeutic actions. This sets the stage for clinical application promising advancements in the wound care arena towards better patient results and quality of life.

Declarations

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

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Conflicts of interest/Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Data availability

The data will be made available upon request.

Credit taxonomy:

Conceptualization: Ms Aishwarya Jain; **Methodology:** Ms Aishwarya Jain, Dr (Mrs) Kiran Bhise; **Formal analysis and investigation:** Ms Aishwarya Jain, Dr (Mrs) Kiran Bhise; **Writing -original draft preparation:** Ms Aishwarya Jain

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Figures

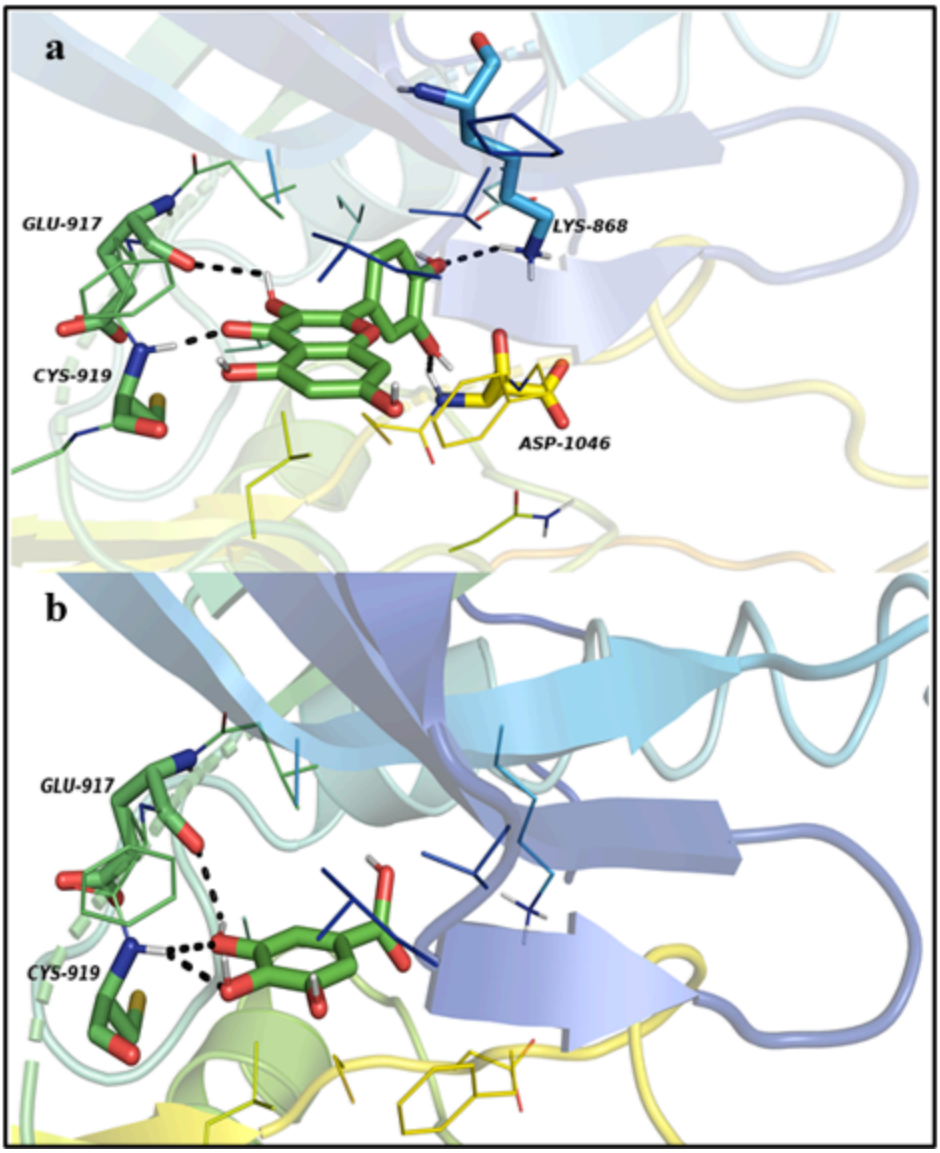

Figure 1

Docking poses of (a) Quercetin and (b) Gallic Acid with VEGFR2.

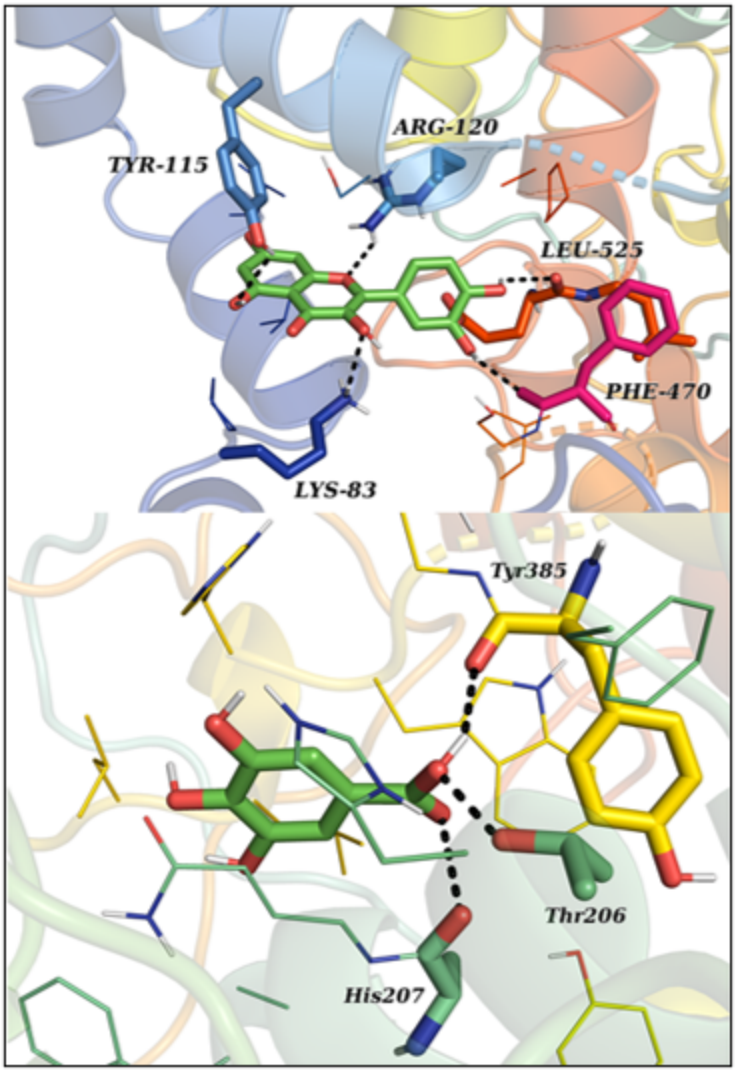

Figure 2

Docking poses of Quercetin and Gallic Acid with COX-2.