RESEARCH ARTICLE

Molecular Docking Analysis of *Potentilla fulgens* Polyphenols against Estrogen Receptors Involved in Breast Cancer

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ABSTRACT

Breast cancer is still a major worldwide health issue, which makes the search for new treatment options necessary. Through their interactions with estrogen receptors (ERs), polyphenolic chemicals from *Potentilla fulgens* may prove to be effective therapeutics for breast cancer treatment. This work investigates this possibility using molecular docking analysis. A curated library of polyphenols was compiled from the PubChem database, ensuring diversity and biological relevance. Crystallographic structures of ERα and ERβ were selected, and molecular docking studies were conducted using the CB-Dock2 server. The results revealed intricate binding affinities, with compounds such as afzelechin, epiafzelechin, epicatechin, and catechin demonstrating robust interactions with both receptors. Structural analysis of cavity pockets in ERα and ERβ unveiled distinct features, highlighting variations in volume, center coordinates, and size. Comparison with the standard tamoxifen indicated nuanced binding patterns, suggesting potential alternatives or complementary agents. Epigallocatechingallate exhibited higher affinity for ERα, while afzelechin (4β→8) epicatechin and epiafzelechin (4β→8) epicatechin showed moderate binding favoring ERβ. These findings provide valuable insights into the molecular interactions of *P. fulgens* polyphenols with ERs, laying the groundwork for the development of targeted interventions for breast cancer.

Keywords: *Potentilla fulgens*, Polyphenols, Breast cancer, Molecular docking, Estrogen receptors.

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INTRODUCTION

Breast cancer continues to be a major global health problem due to its rising incidence and profound effects on millions of lives.[1-4] The search for novel and effective therapeutic agents is a constant endeavor, and natural compounds have garnered considerable attention due to their diverse pharmacological properties. *Potentilla fulgens*, an herbaceous plant native to the Himalayan region, has been traditionally used for its medicinal properties. In particular, the polyphenolic constituents of *P. fulgens* have demonstrated antioxidant and anti-inflammatory activities, suggesting their potential in combating various diseases, including cancer.[5-7]

Because of their critical involvement in the initiation and spread of breast cancer, estrogen receptors (ERs) are desirable targets for therapeutic intervention. The growth and survival of hormone receptor-positive breast tumors are linked to estrogen signaling, underscoring the importance of creating targeted medicines to alter ER activity. In this context, molecular docking analysis emerges as a powerful computational tool for predicting the binding affinity and interaction modes of small molecules with target proteins, offering insights into their potential as therapeutic agents.[8,9]

This research paper aims to explore the molecular interactions between *P. fulgens* polyphenols and estrogen receptors through *in-silico* molecular docking studies. We employ advanced computational techniques. The overarching goal is to identify specific polyphenolic compounds that exhibit promising interactions with estrogen receptors, laying the

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foundation for their potential as therapeutic candidates for breast cancer.

Through this investigation, we hope to contribute valuable information to the growing body of knowledge surrounding natural compounds and their potential role in breast cancer treatment. Integrating computational approaches with traditional pharmacological research offers a comprehensive strategy for identifying novel therapeutic agents, bridging traditional medicine and modern drug discovery. As we delve into the intricate molecular landscape of *P. fulgens* polyphenols and estrogen receptors, our findings may pave the way for the development of targeted and effective interventions for breast cancer, addressing the critical need for innovative approaches in the fight against this formidable disease.

MATERIALS AND METHODS

Collection and Preparation of *P. fulgens* Polyphenols

For the collection and preparation of a library of selected *P. fulgens* polyphenols, the procedure involved accessing and retrieving chemical information from the PubChem database. Initial searches were conducted on the PubChem platform to identify relevant chemical compounds present in *P. fulgens*. The search queries focused on polyphenols specific to *P. fulgens*, utilizing both common and scientific names to ensure comprehensive coverage. Chemical structures, identifiers, and associated data for the identified polyphenols were extracted from the PubChem database.[10]

Subsequently, the collected compounds underwent curation to ensure data consistency and reliability. Redundant or irrelevant entries were excluded, and chemical structures were verified for accuracy. Standardized nomenclature and chemical identifiers, such as InChI and SMILES notation, were assigned to each compound to facilitate uniformity and compatibility in subsequent computational analyses.

Various subclasses and structural variations within the polyphenol family were considered to enhance the diversity of the polyphenol library. Special attention was given to compounds with documented biological relevance and anticancer potential. The resulting library constituted a curated set of *P. fulgens* polyphenols prepared for subsequent molecular docking studies on estrogen receptors. The compilation of this library from the PubChem database serves as a foundation for the *in-silico* investigation into the potential anti-breast cancer properties of *P. fulgens* polyphenols (Table 1).

Table 1: List of polyphenolic compound found in *P. fulgens*[15]

No.	*Polyphenolic compound*
1.	Afzelechin
2.	Epiafzelechin
3.	Epigallocatechin
4.	Epigallocatechingallate
5.	Epicatechin
6.	Catechin
7.	Afzelechin (4β→8) epicatechin
8.	Epiafzelechin (4β→8) epicatechin
9.	Catechin (4α→8) epicatechin
10.	Afzelechin (4α→8) catechin
11.	Afzelechin (4α→8) epiafzelechin

Selection of Estrogen Receptor Structures

Crystallographic structures of estrogen receptors, both estrogen receptor alpha (ERα) (PBD ID: 1X7J) and estrogen receptor beta (ERβ) (PBD ID: 1X7R), were retrieved from reputable protein databases such as the Protein Data Bank (PDB) (Figure 1). Selection criteria included high resolution and relevance to breast cancer.[11]

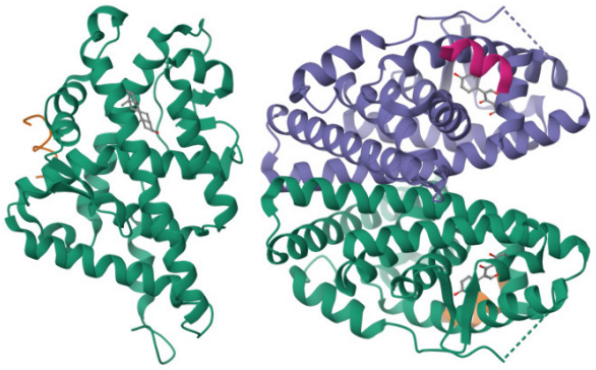

Figure 1: Crystallographic structures A) estrogen receptor alpha (ERα) B) estrogen receptor beta (ERβ)

Molecular Docking Studies

To unlock the potential of *P. fulgens* polyphenols as breast cancer therapy, CB-Dock2 server was utilized for the deep dive into their interactions with estrogen receptors. The process began by uploading prepared protein and ligand files, prompting the server to search for similar ligands and evaluate protein compatibility. Suitable protein-ligand complexes emerged, guiding the template-based cavity detection and docking powered by FitDock. Meanwhile, a Perl script orchestrated the process, employing AutoDock Vina and BioLip for independent and template-driven docking. Retrieved results were meticulously analyzed for poses and key data (Tables 2 and 3).[12-14]

RESULTS

Results of Collection and Preparation of *P. fulgens* Polyphenols

The approach resulted in a collection of meticulously chosen polyphenols from *P. fulgens*, which were subsequently prepared for utilization in molecular docking tests involving estrogen receptors. The *in-silico* investigation of the potential anti-breast cancer properties of polyphenols derived from *P. fulgens* is based on the construction of this library from the PubChem database.

Results of Molecular Docking

The analysis of the cavity pockets in estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) reveals

Table 2: Details of cavity pockets found in estrogen receptor alpha and beta

Cavity	*Receptor*	*Cavity volume (Å³)*	*Center (x, y, z)*	*Cavity size (x, y, z)*
C1	ERα	2200	50, 42, 6	20, 24, 15
C2	ERα	956	28, 52, 17	13, 13, 11
C3	ERα	394	57, 30, 26	10, 12, 8
C4	ERα	191	34, 33, 8	11, 8, 8
C5	ERα	85	45, 27, 17	5, 7, 6
C1	ERβ	609	10, 27, 12	13, 10, 11
C2	ERβ	391	16, 32, 22	9, 9, 11
C3	ERβ	146	37, 14, 15	6, 9, 7
C4	ERβ	136	30, 29, 12	7, 8, 14
C5	ERβ	119	29, 14, 21	7, 8, 6

Table 3: Results of molecular docking studies

No.	*Polyphenolic compound*	*Autodock vina score (estrogen receptor alpha)*	*Autodock vina score (estrogen receptor beta)*
1.	Tamoxifen (standard)	-7.8	-6.8
2.	Afzelechin	-8.8	-8.8
3.	Epiafzelechin	-8.8	-8.8
4.	Epigallocatechin	-7.8	-8.6
5.	Epigallocatechingallate	-8.4	-8.0
6.	Epicatechin	-8.7	-8.5
7.	Catechin	-8.7	-8.5
8.	Afzelechin (4β→8) epicatechin	-7.9	-8.3
9.	Epiafzelechin (4β→8) epicatechin	-8.1	-8.6
10.	Catechin (4α→8) epicatechin	-7.3	-8.4
11.	Afzelechin (4α→8) catechin	-7.5	-8.5
12	Afzelechin (4α→8) epiafzelechin	-8.0	-8.5

distinct structural features (Figures 2 and 3). In ERα, C1 exhibits the largest cavity volume; in ERβ, C1 also has the largest volume.[16,17] The coordinates of cavity centers differ between the receptors, indicating spatial variations in their binding sites. Additionally, the cavity sizes exhibit differences, emphasizing unique structural characteristics in the two receptors. These cavity volumes and size variations suggest potential ligand binding and substrate recognition differences.[18,19] Understanding these structural nuances is vital for designing selective ligands and comprehending the nuanced interactions of compounds with ERα and ERβ, contributing to the development of targeted therapeutic interventions. Further studies, such as molecular docking, can delve into the functional implications of these cavity characteristics in ligand-receptor interactions.[20,21]

In summary, the analysis of the polyphenolic compounds' interactions with estrogen receptors alpha (ERα) and beta (ERβ) reveals a nuanced pattern of binding affinities over standard tamoxifen. Compounds such as afzelechin, epiafzelechin, epicatechin, and catechin consistently exhibit robust binding

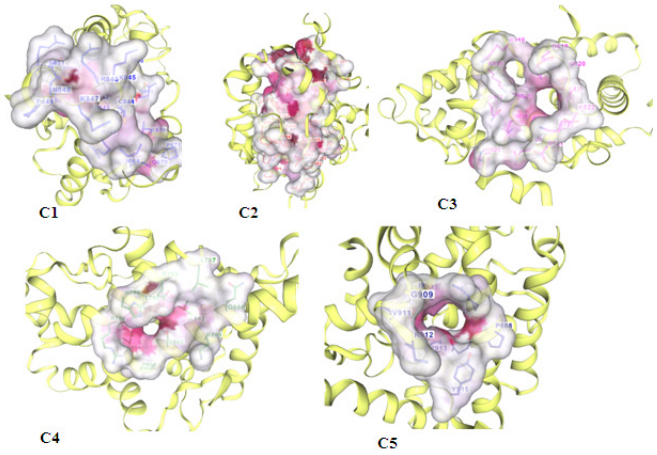

Figure 2: Cavities detected in estrogen receptor alpha

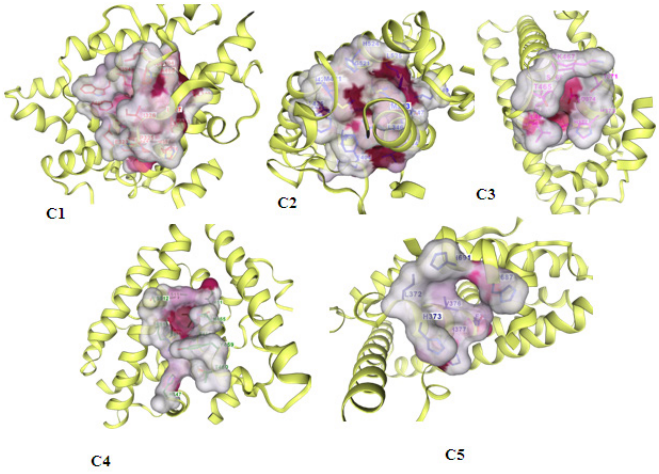

Figure 3: Cavities detected in estrogen receptor beta

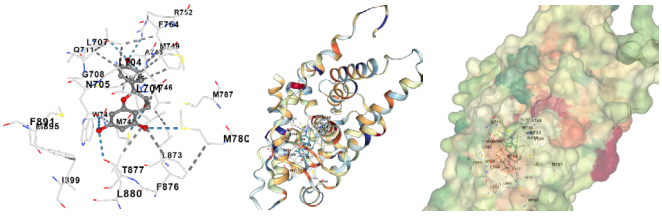

Figure 4: Interactions of afzelechin and epiafzelechin with estrogen receptor alpha

to both receptors, suggesting their potential influence on estrogen receptor signaling pathways. The specificity of amino acid interactions in each receptor pocket underscores the unique molecular signatures contributing to the compounds' binding affinities. Notably, epigallocatechingallate exhibits a marginally higher affinity for ERα, while afzelechin (4β→8) epicatechin and epiafzelechin (4β→8) epicatechin demonstrate moderate binding favoring ERβ (Figures 4 and 5).[22,23]

These findings contribute valuable insights into the intricate interactions between polyphenolic compounds and estrogen receptors, laying the groundwork for further exploration of their potential therapeutic implications. Understanding the

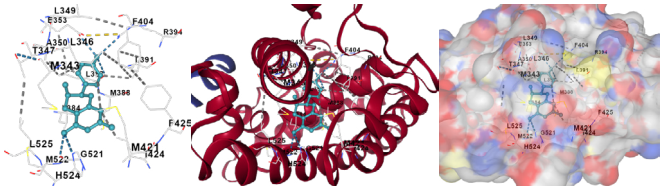

Figure 5: Interactions of afzelechin and epiafzelechin with estrogen receptor beta

differential binding affinities of these compounds for ERα and ERβ can inform future research aimed at developing targeted interventions for conditions influenced by estrogen signaling, such as hormone-related cancers and metabolic disorders. Additionally, this knowledge may guide the design of novel compounds with optimized binding profiles for specific estrogen receptor subtypes, opening avenues for the development of more effective and selective therapeutic agents.[24,25]

CONCLUSION

In conclusion, this research focused on elucidating the interactions between selected polyphenolic compounds from *P. fulgens* and estrogen receptors alpha (ERα) and beta (ERβ) through comprehensive molecular docking studies. The process involved the curation of a polyphenol library from *P. fulgens*, ensuring diverse representation and biological relevance. Crystallographic structures of ERα and ERβ were selected based on high resolution and relevance to breast cancer. Molecular docking studies, facilitated by the CB-Dock2 server, unveiled intricate binding affinities of the polyphenolic compounds to the estrogen receptors. Notably, compounds such as afzelechin, epiafzelechin, epicatechin, and catechin demonstrated robust binding to both receptors, emphasizing their potential influence on estrogen receptor signaling pathways.

The analysis of cavity pockets in ERα and ERβ revealed distinct structural features, including variations in volume, center coordinates, and size. These structural nuances underscore the unique molecular signatures contributing to the compounds' binding affinities. Furthermore, the study compared the binding affinities of polyphenolic compounds with the standard tamoxifen, revealing nuanced patterns that suggest potential alternatives or complementary agents for breast cancer therapy. Specifically, epigallocatechingallate exhibited a marginally higher affinity for ERα, while afzelechin (4β→8) epicatechin and epiafzelechin (4β→8) epicatechin showed moderate binding favoring ERβ.

These findings contribute valuable insights into the complex interactions between polyphenolic compounds and estrogen receptors, providing a foundation for further exploration of their therapeutic implications. Understanding the specificity of amino acid interactions within receptor pockets informs the design of compounds with optimized binding profiles for specific estrogen receptor subtypes. This research paves the way for the development of more effective and selective therapeutic agents tailored to conditions influenced by estrogen signaling, such as hormone-related cancers and metabolic disorders. The detailed molecular insights gained from this study enhance our understanding of the potential pharmacological benefits of *P. fulgens* polyphenols in breast cancer treatment.

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