RESEARCH ARTICLE

Moracin Flavonoids-based Virtual Screening Using Extended Reduced Graph Fingerprints Pharmacophore for COX-1 and PDES Targeting in Breast Cancer

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ABSTRACT

In order to create successful treatments for breast cancer, it is crucial to understand the binding interactions between flavonoids and phosphodiesterase (PDEs) and cyclooxygenase 1 (COX-1). This study uses computational methods to achieve just that. For the purpose of treating breast cancer, this study offers a thorough computational approach for finding possible COX-1 and PDEs inhibitors. Starting with the selection of bioactive compounds from the ChMBI database, the study makes use of a combination of pharmacophore-based and structural techniques. To perform molecular docking simulations with the indicated medicines, the PDB-REDO refined PDE4B2B and human COX-1 crystal structure were utilized. The binding affinities and interaction patterns of particular drugs with the COX-1 and PDEs are revealed by molecular docking simulations performed with the AutoDock program. The virtual screening results indicate that compounds with attractive interaction patterns, high binding affinities, and good structural compatibility could be good lead candidates. ADMET lab 2.0 tool for filtration was used to guarantee safety and effectiveness, offering information on the toxicity profile and pharmacokinetic characteristics of the chemical compound. Across numerous toxicity classes and endpoints, the chosen chemical, moracin C (C19H18O4), shows an anticipated inactivity and a largely good safety profile. Although immunotoxicity is anticipated, the overall low likelihood points to a comparatively modest risk. Moracin C has the potential to be developed into a medication, according to physicochemical and pharmacokinetic evaluations.

Keywords: COX-1, PDEs, ErG fingerprints pharmacophore, ChEBI database, Molecular docking, Virtual screening, Breast cancer.

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Conflict of interest: None

INTRODUCTION

Timely detection is crucial for the prevention of breast cancer, which ranks as the second leading cause of cancer-related fatalities among women. Recent advancements in our comprehension of the condition and the creation of preventive strategies have revealed the underlying mechanisms, drug-resistant mechanisms, and disease-related genes. Today, there is a wider range of pharmacological options accessible to improve patients' quality of existence through biological and chemoprevention.[1] Breast cancer is a worldwide problem, and in South Africa, there are big differences in survival, screening, and treatment. Incidence has grown over the previous 20 years, leading to disparities in healthcare and delayed diagnosis. Human immunodeficiency virus (HIV) and breast cancer co-occurring complicate problems, especially for black people. Robust screening programs, prompt treatment initiation, and customized interventions are needed to address these discrepancies. To address these complex discrepancies and enhance breast cancer care throughout the African continent, pan-African research and collaboration are required.[2]

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It has been discovered that flavonoids affect signal transduction pathways in the formation of cancer and have anticancer activities. By controlling cell metabolism they stop diseases from spreading. A diet high in flavonoids is one possible way to prevent cancer. With fewer side effects than traditional medication, flavonoids are a promising chemopreventive chemical that can be used in conjunction with other therapies to treat breast cancer. They also demonstrate pleiotropic and multi-target actions. The several pleiotropic pharmacological effects of different flavonoids on breast cancer are highlighted in this study.[3]

Enzymes called phosphodiesterases (PDEs) are involved in a number of physiological activities. They consist of eleven families with distinct subtypes that differ in terms of distribution, expression, and inhibitor sensitivity. PDEs play a role in various pathological developments such as depression, asthma, cancer, and inflammation. Studies reveal that PDEs influence intracellular cAMP and/or cGMP levels, which may act as indicators for diagnosis or targets for treatment.[4]

Prostaglandins are made from arachidonic acid by the primary enzyme cyclooxygenase (COX). COX-1 and COX-2 are the two isoforms. COX-2 is induced in response to growth factors and proinflammatory cytokines, whereas COX-1 is produced constitutively in a variety of organs. Breast cancer development may be influenced by elevated COX-2 expression. Because selective inhibitors of COX-1 stop the growth of breast tumor cells and their ability to spread, COX-1 may also be involved in the development of breast cancer.[5]

MATERIALS AND METHODS

Selection Compound for Virtual Screening

The preferred compound molecular structure displayed in Figure 1 is selected based on literature showing its importance in cancer management.

Bioactive Compound Database

The ChEBI database was our main tool for locating bioactive compounds. ChEBI is an extensive database of bioactivity information that includes a wide variety of compounds with established biological roles.

Pharmacophore-based Screening

We employed extended reduced graph fingerprints (Pharmacophore) screening methodology to identify possible COX-1 and PDEs inhibitors. The approach comprises determining the essential pharmacophore characteristics needed for COX-1 and PDEs inhibition and screening medications to make sure they meet these requirements.[6]

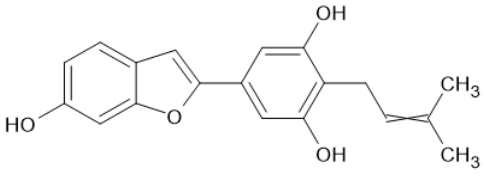


Figure 1: 2D structure of moracin C

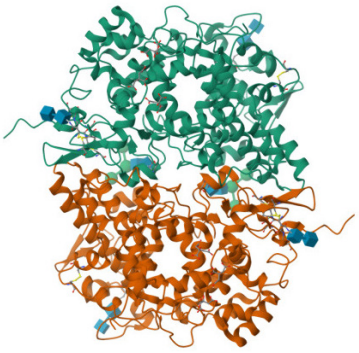


Figure 2: Structure of COX-1 protein

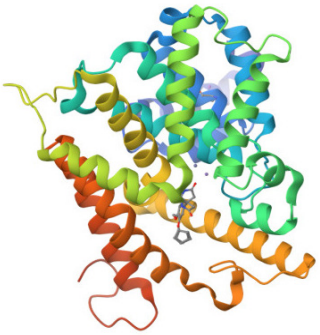


Figure 3: Structure of PDE4B2B protein

Preprocessing of Protein Structure

The protein structure of Human COX-1 and PDE4B2B is depicted in Figures 2 and 3, respectively, in PDB format with the corresponding PDB IDs 6Y3C and 1RO6. The data was acquired from the website https://www.rcsb.org/ and prepared using the website's server PDB-REDO version 8.01.[7]

Molecular Docking

Molecular docking simulations have been employed to assess how well certain drugs are bound to the COX-1 and PDEs receptors and how they interact.

Molecular docking studies were performed using cb dock two server a widely used and robust tool for predicting the binding affinity and mode of small molecules with their target proteins.

Docking Protocol

Grid box setting

The grid box was centered on the ligand-binding domain of the AR with dimensions large enough to encompass the entire binding pocket.

Ligand preparation

The optimized flavanone structures were converted to PDBQT format using AutoDockTools.

Docking simulation

Each flavanone was docked into the AR binding site using AutoDock Vina. The exhaustiveness parameter was set to 8 to ensure a thorough exploration of the binding conformations.[8]

Analysis of docking results

The docking results were analyzed based on the binding affinity (measured in kcal/mol) and the interaction profiles. The top-ranked poses for each flavanone were examined for hydrogen bonding, hydrophobic interactions, and other relevant binding interactions with the AR. Visualization and analysis were carried out using PyMOL and Discovery Studio Visualizer.

ADME-T prediction

To conduct toxicity prediction studies, we utilized the SwissADME server and Protox-II. Firstly, we gathered data on chemical compounds, including their structures and ChEBI IDs. Then, we input these compounds into SwissADME, assessing toxicity across various endpoints. Next, using Protox-II, we analyzed potential adverse effects, focusing on organ toxicity and molecular pathways. Results were compared, discrepancies noted, and findings summarized, aiding informed decision-making in drug development.[9]

RESULTS AND DISCUSSION

Results of Pharmacophore-based Screening Studies

Table 1 presents the results of pharmacophore-based screening conducted by the Swiss similarity server, listing ChEBI IDs and corresponding 2D structures of the compounds. The structures of compounds are analyzed based on their molecular features to identify potential ligands that interact with a target receptor or enzyme.

Results of Refinement of Protein Structures

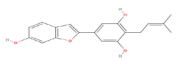
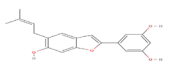
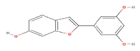
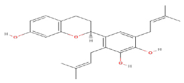
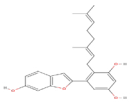
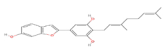
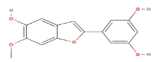
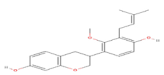
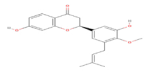
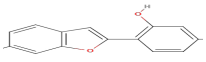
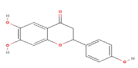
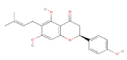
The crystallographic structure of phosphodiesterase (PDEs) with PDB ID 1RO6 underwent refinement using PDB-REDO, resulting in improvements in various validation metrics. The original refinement yielded R and R-free values of 0.2155 and 0.2547, respectively. After PDB-REDO refinement, these values improved significantly to 0.1675 and 0.1951, indicating enhanced agreement between the experimental data and the refined model. Moreover, the bond length and angle RMS Z-Scores also showed improvements, with values increasing from 0.292 to 0.495 and from 0.607 to 0.722, respectively.

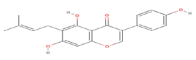
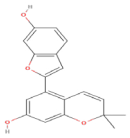
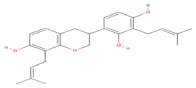
Validation metrics from PDB-REDO refinement further demonstrated enhancements in model quality. The Ramachandran plot normality improved notably from 60 to 96%, indicating a higher percentage of residues falling within the favored regions of the Ramachandran plot. Similarly, the rotamer normality increased from 62 to 87%, indicating improved side-chain conformations. Coarse packing and fine packing scores also showed enhancements, with increases from 89 to 93% and from 72 to 81%, respectively.

However, the bump severity score exhibited a decrease from 74 to 26%, suggesting a reduction in steric clashes within the refined model. On the other hand, hydrogen bond satisfaction showed a slight improvement from 78 to 85%.

Regarding WHAT_CHECK analysis, the Ramachandran Z-score and the assessment of preferred, allowed, and outlier regions were not provided in the original refinement but were included after PDB-REDO refinement. These metrics further

Table 1: Results of pharmacophore-based screening by Swiss similarity server

S. No.	*ChEBI ID*	*2D structure*
1.	CHEBI: 174235	
2.	CHEBI: 174237	
3.	CHEBI: 174251	
4.	CHEBI: 6118	
5.	CHEBI: 2543	
6.	CHEBI: 174998	
7.	CHEBI: 174574	
8.	CHEBI: 175318	
9.	CHEBI: 65865	
10.	CHEBI: 169055	
11.	CHEBI: 78026	
12.	CHEBI: 27566	

13.	CHEBI: 10038	
14.	CHEBI: 174943	
15.	CHEBI: 172632	

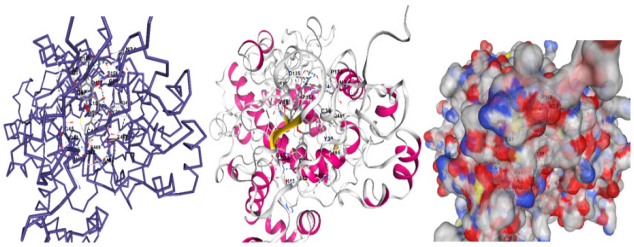


Figure 4: Interaction of CHEBI: 10038 with 6Y3C

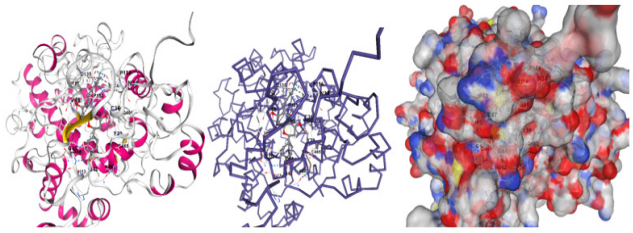


Figure 5: Interaction of CHEBI: 10038 with 1RO6

underscored the improvements in model quality achieved through PDB-REDO refinement.

The application of PDB-REDO refinement to the crystallographic structure of phosphodiesterase (PDEs) [PDB ID: 1RO6] resulted in significant enhancements in various validation metrics, including R and R-free values, bond length and angle RMS Z-Scores, and model quality scores such as Ramachandran plot normality and rotamer normality. These improvements indicate a higher quality and accuracy of the refined model, with better agreement between the experimental data and the refined structure. Overall, the findings highlight the efficacy of PDB-REDO refinement in optimizing crystallographic structures and enhancing their reliability for further structural and functional studies.

The original refinement yielded R and R-free values of 0.2299 and 0.2774, respectively. After PDB-REDO refinement, these values slightly increased to 0.2433 and 0.2850, indicating a marginal decrease in the agreement between the experimental data and the refined model. However, the improvements in bond length and angle RMS Z-Scores were more notable, with values increasing from 0.202 to 0.446 and from 0.548 to 0.708, respectively.

Regarding model quality metrics, both raw scores and percentiles showed modest enhancements in various aspects. The Ramachandran plot normality and rotamer normality scores increased marginally from 7 to 9% and from 32 to 34%, respectively. Coarse packing remained consistent at 3%, while fine packing showed a notable increase from 7 to 26%. However, bump severity exhibited a considerable increase from 2 to 37%, indicating a higher occurrence of steric clashes within the refined model. Hydrogen bond satisfaction also showed a slight increase from 5 to 6%.

Unfortunately, specific metrics such as the Ramachandran Z-Score and the assessment of preferred, allowed, and outlier regions were not provided in the original refinement but were not included after PDB-REDO refinement.

The refinement of the crystallographic structure of cyclooxygenase-1 (COX-1) [PDB ID: 1RO6] using PDB-REDO resulted in mixed improvements in validation metrics. While there were marginal increases in R and R-free values, the enhancements in bond length and angle RMS Z-Scores were more significant. Model quality metrics showed modest improvements in some aspects, such as fine packing, but also revealed a notable increase in bump severity, indicating a higher occurrence of steric clashes within the refined model. Overall, the findings suggest that while PDB-REDO refinement contributed to some enhancements in the structural quality of COX-1, further optimization may be necessary to address certain structural issues and improve overall model reliability.

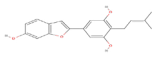
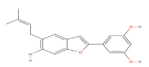
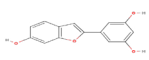
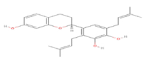
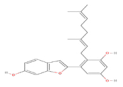
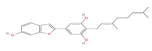
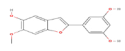
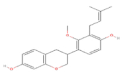
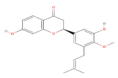
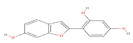
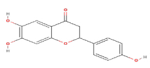
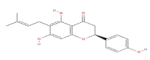
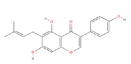
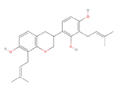
Results of Docking Studies

The data shown in Table 2 presents CB-Dock scores for various compounds across two different proteins, 6Y3C and 1RO6. Figures 4 and 5 give an intraction overview of Notably, compounds such as CHEBI: 10038 demonstrate consistently low CB-Dock scores across both proteins, indicating strong binding affinity. Conversely, compounds like CHEBI: 78026 exhibit higher scores, suggesting weaker binding. While some compounds display consistent scores across both proteins, others show variability, indicating potential differences in interaction patterns between the proteins.[10] These findings underscore the importance of considering protein selectivity in drug design. Moreover, compounds with consistently low scores may warrant further investigation as potential lead compounds due to their strong binding affinity.[11] Overall, the analysis provides valuable insights into the binding characteristics of compounds and can guide the selection of lead compounds for drug development efforts.[12,13]

Results of Toxicity Prediction Studies

The predictions are categorized into organ toxicity, toxicity endpoints, Tox21-nuclear receptor signaling pathways, and Tox21-stress response pathways.[14,15] For instance, in

Table 2: Results obtained after docking experiments

S. No.	*ChEBI ID*	*2D structure*	*CB-Dock Score [6Y3C]*	*CB-Dock Score [1RO6]*
1.	CHEBI: 174235		-9.8	-9.2
2.	CHEBI: 174237		-9.0	-9.2
3.	CHEBI: 174251		-8.8	-8.4
4.	CHEBI: 6118		-7.9	-9.7
5.	CHEBI: 2543		-9.5	-10.2
6.	CHEBI: 174998		-9.3	-9.0
7.	CHEBI: 174574		-8.5	-8.1
8.	CHEBI: 175318		-8.6	-8.2
9.	CHEBI: 65865		-8.2	-8.8
10.	CHEBI: 169055		-8.8	-7.8
11.	CHEBI: 78026		-7.8	-8.3
12.	CHEBI: 27566		-9.3	-9.0
13.	CHEBI: 10038		-10.0	-9.8
14.	CHEBI: 174943		-8.7	-9.7
15.	CHEBI: 172632		-8.8	-9.6

organ toxicity, CHEBI: 27566 is predicted to be inactive for hepatotoxicity, neurotoxicity, and cardiotoxicity, with probabilities of 0.69, 0.79, and 0.98, respectively. However, it is predicted to be active for nephrotoxicity and respiratory toxicity, with probabilities of 0.58 and 0.79, respectively. In toxicity endpoints, CHEBI: 27566 is inactive for carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, BBB-barrier, and ecotoxicity, with varying probabilities. Notably, it is active for clinical toxicity and nutritional toxicity, with probabilities of 0.59 and 0.62, respectively. In Tox21-nuclear receptor signaling pathways and Tox21-stress response pathways, CHEBI: 27566 is predominantly inactive across various targets, except for mitochondrial membrane potential (MMP), where it is active with a probability of 0.69.

CHEBI: 27566 exhibits diverse toxicity predictions across different endpoints, indicating its potential effects on various organ systems and molecular pathways. While it is largely inactive for organ toxicity endpoints such as hepatotoxicity and cardiotoxicity, it shows activity for nephrotoxicity and respiratory toxicity. In toxicity endpoints, CHEBI: 27566 is predicted to be inactive for carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity, suggesting a lower risk of adverse effects in these areas. However, it is active for clinical toxicity and nutritional toxicity, indicating potential adverse effects on clinical parameters and nutritional pathways. In Tox21-nuclear receptor signaling pathways and Tox21-stress response pathways, CHEBI: 27566 demonstrates predominantly inactive predictions, highlighting its minimal impact on these molecular pathways.[16]

CONCLUSION

The comprehensive pharmacophore-based screening, protein structure refinement, docking studies, and toxicity predictions have yielded significant insights into potential lead compounds for drug development. The screening identified 15 compounds from the ChEBI database with unique molecular features. Compounds such as CHEBI: 174235, CHEBI: 174237, and others were selected based on their structural compatibility with the target receptor, highlighting their potential as effective ligands. The refinement of the crystallographic structure of phosphodiesterase (PDEs) with PDB ID 1RO6 using PDB-REDO showed notable improvements in validation metrics. The R and R-free values decreased from 0.2155 and 0.2547 to 0.1675 and 0.1951, respectively, indicating better model accuracy. Enhancements in bond length and angle RMS Z-scores, from 0.292 to 0.495 and 0.607 to 0.722, respectively, further validate the improved model quality. The Ramachandran plot normality increased from 60 to 96%, and the rotamer normality risen from 62 to 87%, indicating a significant improvement in structural quality.

Docking experiments using CB-Dock provided scores for various compounds across two proteins, 6Y3C and 1RO6. For instance, CHEBI: 10038 showed a strong binding affinity with low CB-Dock scores of -10.0 for 6Y3C and -9.8 for 1RO6. Conversely, CHEBI: 78026 had higher scores of -7.8 and -8.3, respectively, suggesting weaker binding. These results emphasize the potential of compounds like CHEBI: 10038 for

further investigation as lead compounds due to their consistent strong binding across different targets.

The toxicity predictions for CHEBI: 27566 revealed its diverse effects on various organ systems and molecular pathways. It is predicted to be inactive for hepatotoxicity, neurotoxicity, and cardiotoxicity with probabilities of 0.69, 0.79, and 0.98, respectively. However, it is active for nephrotoxicity and respiratory toxicity, with probabilities of 0.58 and 0.79, respectively. For toxicity endpoints, it is inactive for carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity but active for clinical and nutritional toxicity with probabilities of 0.59 and 0.62, respectively. This indicates a balanced profile of potential adverse effects that need to be addressed in further studies.

In conclusion, the integration of pharmacophore-based screening, structural refinement, docking studies, and toxicity predictions has provided a robust framework for identifying and optimizing potential drug candidates. Compounds such as CHEBI: 10038 and CHEBI: 27566 demonstrate promising characteristics that warrant further investigation and development. The improved structural models and detailed binding affinities underscore the importance of these methods in advancing drug discovery efforts.

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