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Exploring Natural Compounds as Promising Matrix Metalloproteinase-2 inhibitors for Cancer Management: A Biocomputational Study

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Abstract

Background: Matrix metalloproteinase-2 (MMP2) plays a role in breaking down the components of the extracellular matrix, which allows cancer cells to advance and invade. Therefore, the inhibition of MMP2 shows potential as a promising strategy for treating cancer.

Methods: This study employed computational screening to identify MMP2 inhibitors from a collection of 2,405 natural compounds. GLXC-26716, the co-crystal ligand of MMP2, served as the positive control. Virtual screening was performed using PyRx 8.0 software to find molecules that might inhibit the active site of MMP2.

Results: The virtual screening process has identified five potential candidates: ZINC000000001412, ZINC000001612328, ZINC000001614079, ZINC000000119988, and ZINC0000000047553. These candidates were selected based on their strong binding affinities and interactions with MMP2. These compounds, which adhere to Lipinski's Rule of Five and have significant physicochemical properties, show promise as MMP2 inhibitors.

Conclusion: The finding of this study indicates a preliminary investigation into an innovative approach for managing cancer that inhibits the invasion and dissemination of cancer cells.

Introduction

Cancer is predominant contributor of disease burden and mortality worldwide [1]. Consequently, the previous two decades of biomedical research have provided a vast reservoir of knowledge about the molecular complexities inherent in carcinogenesis and the signaling pathways intricately involved in cancer growth. The molecular processes that orchestrate the complicated interplay between cancerous cells and the tumor microenvironment exhibit a critical role in this progression [2].

It has been shown that extracellular matrix (ECM) remodeling proteinases, particularly matrix metalloproteinases (MMPs), are key mediators of microenvironmental changes during cancer progression [2,3]. MMPs are zinc-dependent endopeptidases that aid wound healing, uterine involution, and organogenesis. They are also linked to inflammatory, vascular, auto-immune, and cancerous conditions [4,5]. MMPs' potential diagnostic and prognostic utility has been recognized across a wide range of cancer types and stages [6]. The correlation between cancer cells' basement membrane degradation and metastatic potential led to the development of MMPs as cancer therapeutic targets 25 years ago [7]. A growing number of MMP inhibitors have been developed and tested in clinical trials.

MMP2 is an example of the distinct roles that individual members of the MMP family play in disease progression. Its significance stems from the comprehensive processing of a wide range of ECM and non-ECM substrates, necessitating a thorough examination of the implications at each stage of the metastatic cascade [7-9]. MMP2's extensive repertoire of substrates, both matrix and non-matrix, cleaves establishes its influential role in multiple steps of the metastatic cascade in breast cancer [10]. Furthermore, increased MMP2 expression emerges as an independent and ominous prognostic indicator for ovarian cancer patients, correlating with lower overall survival rates [11]. MMP2 overexpression has also been identified as a potential predictor of poor prognosis in gastric cancer patients [12]. Hence, targeting MMP2 as a therapeutic hold promise across a wide range of cancer types. The study employed in-silico structure-based virtual screening to identify natural MMP2 inhibitors to discover compounds capable of inhibiting MMP2, a pivotal enzyme implicated in cancer advancement.

Methods

Target protein preparation

The 3D structure of MMP2 (PDB ID: 8H78) was acquired from the protein data bank. The heteroatoms, including the water molecules and four ligands (zinc ion, calcium ion, dihydrogen phosphate ion, and ligand L2U (GLXC-26716)), were eliminated. The cleaned structure was then optimized using UCSF Chimera software in preparation for subsequent docking analysis.

Natural compound library preparation

A subset of 2,405 natural compounds that meet Lipinski's Rule of Five (Ro5) criteria have been retrieved from the ZINC database, which provides data in SDF (Structure-Data File) format. The geometries of these compounds were subsequently optimized by performing energy minimization using the Universal Force Field (UFF). After undergoing minimization, the compounds have been converted into PDBQT format using the PyRx software, enabling subsequent docking investigations and interaction analysis.

Structure-based virtual screening

Virtual screening (VS) is an important part of the drug design and discovery pipeline. It entails using molecular docking methodologies to evaluate a large number of potential ligands to determine which have the highest affinity for binding to the target protein. Compared to traditional experimental screening methods, this approach offers a significant advantage in terms of time and resource efficiency [13,14]. Top-ranking compounds are then subjected to additional experimental testing, which aids in the identification of potential hits [15,16]. In this study, the prepared natural compound library was screened against the active pocket of MMP2 protein using the PyRx 8.0 software [17].

Results

The prepared library of natural compounds was screened to identify compounds that interact with the binding pocket of the MMP2 protein. This screening resulted in the discovery of 231 compounds that have binding energies similar to or greater than the control compound, GLXC-26716. The binding poses of GLXC-26716 were analyzed using Discovery Studio (DS), which led to the accurate determination of the binding pocket's coordinates at 26.172047 (X), 23.169750 (Y), and -9.087125 (Z).

Analysis of interactions, both 2D and 3D, along with visual inspection of docked complexes through PyMol and DS, revealed the top 10 hits. These hits showed better binding to MMP2's active site residues compared to the control compound, which had a binding energy of -7.6 kcal/mol. The compounds listed in Table 1 exhibit higher energy values and demonstrate effective H-bond interactions with the target protein.

The top 10 hits identified during the screening exhibited not only higher binding affinity but also demonstrated compelling drug-like characteristics, rendering them suitable as potential drug molecules.

The key physicochemical properties of the five selected compounds were predicted, including Molecular Weight (Mol. Wt.), LogP (Mol.LogP), number of Hydrogen Acceptors (H.A.), Hydrogen Donors (H.D.), Rotatable Bonds, and Total Polar Surface Area (TPSA). These parameters are critical for assessing the compounds' drug-likeness and pharmacokinetic properties, which provide valuable information about their potential efficacy and safety as therapeutic agents. Table 2 presents the physicochemical characteristics, which are crucial in assessing the suitability of a substance as a treatment.

Sr. No.	Top hits	Binding affinity (kcal/mol)
1.	ZINC000000001412	-9.7
2.	ZINC000001612328	-8.9
3.	ZINC000001614079	-8.7
4.	ZINC000000119988	-8.6
5.	ZINC000000047553	-8.4
6.	ZINC000001611274	-8.3
7.	ZINC000001530575	-8.1
8.	ZINC000001614080	-7.8
9.	ZINC000001531846	-7.8
10.	ZINC000001531885	-7.8
11.	GLXC-26716 (Positive control)	-7.6

Table 1: List of top 10 hits and their respective binding energies.

This study performs a comprehensive analysis of the interactions between the target protein's active site residues and the top five hits (ZINC000000001412, ZINC000001612328, ZINC000001614079, ZINC000000119988, and ZINC000000047553) (Figure 1).

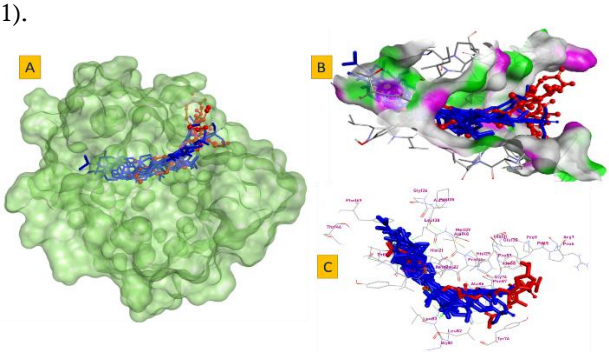

Figure 1: 3D representation of the interaction of the screened top compound with the active pocket of MMP2. A) presents a surface view of the protein with the identified hits, B) highlights the ligands' surrounding surface indicating hydrogen bond donors and acceptors, and C) depicts MMP2 residues interacting with the selected ligands.

Figure 1 illustrates that the five compounds selected via virtual screening, depicted in blue, as well as the positive control used in the study, depicted in red, exhibit binding in almost identical pockets. The interactions between the compounds and the active site of MMP2 show a significant overlap in their common residues, indicating their potential relevance and specificity. This similarity is comparable to that of the control.

The 2D interaction analysis conducted using the DS visualizer for the five compounds and the control compound, as illustrated in Figure 2, demonstrates that most of these compounds have multiple interacting residues with the MMP2 active site. This resemblance implies that these compounds have the potential to accurately imitate the interaction between the control compound and MMP2.

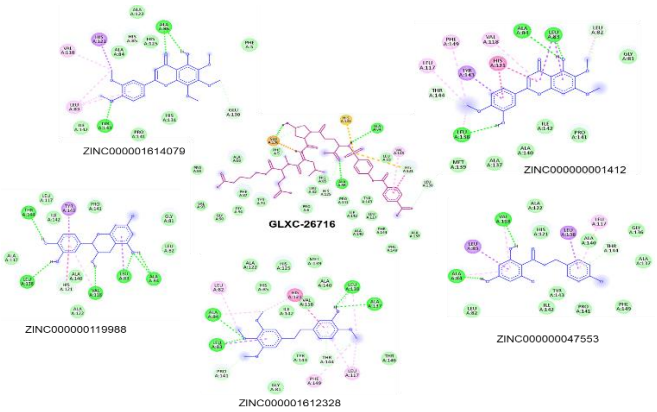

Figure 2: 2D interaction of the top 5 hits and control compound with the MMP2.

The compound ZINC000000001412 had the best binding energy of -9.7 kcal/mol, indicating the highest binding affinity for the MMP2 protein. ZINC000001612328 had a value of -8.9 kcal/mol, while ZINC000001614079, ZINC000000119988, and ZINC000000047553 had values of -8.7 kcal/mol, -8.6 kcal/mol, and -8.4 kcal/mol, respectively. These compounds had significant interactions with a number of key residues in MMP2's active site, including ALA86, ALA84, LEU83, LEU138, VAL118, ALA137, HIS121, GLU130, HIS131, LEU138, THR144, TYR143, PHE149, and HIS125. These interactions demonstrate how these compounds can effectively influence and regulate MMP2 activity.

Discussion

Cancer develops through a multifaceted process that includes mutation, proliferation, survival, invasion, and metastasis. Among the various characteristics of cancer, metastasis is regarded as the pivotal feature, accounting for the vast majority of cancer-related fatalities. MMPs, which are implicated in the metastatic process, represent a promising and novel therapeutic target in this context [18]. MMP2 can cleave various ECM components enzymatically. The degradation of the ECM is recognized as a critical factor in the progression, invasion, and metastasis of different cancers. Hence, inhibiting MMP2 is a potentially promising therapeutic strategy for cancer treatment [19].

Top hits	smile ID	Mol. Wt.	Mol.Log P	H.A.	H.D.	Rotatable Bonds	TPSA
ZINC000000001412	COc1ccc(-c2cc(=O)c3c(O)c(OC)c(OC)cc3o2)cc1O	344.319	2.897	7	2	4	98.36
ZINC000000119983	Oc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)[C@@H](O)C2	290.271	1.5461	6	5	1	110.38
ZINC000001611274	CC[C@@]1(O)C(=O)OCc2c1cc1n(c2=O)Cc2cc3c(CN(C)C)c(O)ccc3nc2-1	421.453	1.8468	8	2	3	104.89
ZINC000001612328	COc1ccc(CCc2cc(OC)c(OC)c(OC)c2)cc1O	318.369	3.2118	5	1	7	57.15
ZINC000000047553	O=C(CCc1ccc(O)cc1)c1c(O)cc(O)cc1O	274.272	2.3245	5	4	4	97.99
ZINC000001530575	COc1cc(CNC(=O)CCCC/C=C/C(C)C)ccc1O	305.418	3.7896	3	2	9	58.56
ZINC000001531846	CCCCC[C@H](O)CC(=O)CCc1ccc(O)c(OC)c1	294.391	3.2338	4	2	10	66.76
ZINC000001614080	COc1ccc(-c2oc3c(OC)c(OC)c(OC)c(OC)c3c(=O)c2OC)cc1OC	432.425	3.5202	9	0	8	94.82
ZINC000001614079	COc1ccc(-c2cc(=O)c3c(O)c(OC)c(OC)c(OC)c3o2)cc1OC	388.372	3.2086	8	1	6	96.59
ZINC000001531885	COc1ccc([C@@H]2OC[C@H]3[C@H]2CO[C@H]3c2ccc(OC)c(OC)c2)cc1OC	386.444	3.7962	6	0	6	55.38

Table 2: Physicochemical properties of the top 10 hits.

This study used computational drug discovery methodology to evaluate the potential inhibitory effects of natural compounds on MMP2.

The selection of natural compounds for this study was primarily based on their drug-like characteristics, following the application of Lipinski's rule of five as a filtering criterion. This guaranteed that the compounds examined were highly probable to possess properties that are appropriate for the development of pharmaceuticals. The strong affinity of the five chosen compounds to the key MMP2 residues through hydrogen bonding, Pi-alkyl interactions, and van der Waals forces underscores their potential as powerful inhibitors of MMP2. These interactions suggest that these compounds have the potential to effectively target MMP2, a crucial enzyme involved in the progression of cancer.

The binding affinity is a crucial parameter determining the extent of interaction between ligand-protein complexes, with a higher negative value indicating strong binding to its target protein [20-23]. Interestingly, the hit compounds (ZINC000000001412, ZINC000001612328, ZINC000001614079, ZINC000000119988, and ZINC0000000047553) exhibited strong binding affinity with MMP2 as compared to the control compound (GLXC-26716), indicating that these hits could be useful as MMP2 inhibitors in cancer therapy.

Contemporary cancer therapies and drugs frequently have negative side effects, making them unsuitable for long-term use. As a result, there is strong support in the medical community for investigating alternative pharmaceutical techniques, particularly those that use natural chemicals. Natural substances, particularly plant-derived phytochemicals, show promise in providing effective cancer treatment while minimizing side effects. Many phytochemicals have inherent bioactivity, making them excellent candidates for improving cancer treatment outcomes [24]. Extensive research has emphasized the importance of phytochemicals in cancer prevention and therapy, with epidemiological studies revealing a possible link between increased phytochemical diet and lower cancer incidence. Experimental research has given light on the processes behind the anticancer activities of phytochemicals, including their capacity to suppress cancer cell proliferation, induce apoptosis and autophagy, and suppress angiogenesis and cancer cell metastasis [25].

The identification and analysis of compounds that have a strong ability to bind to MMP2 and interact specifically with its active site residues offer promising prospects for the development of anticancer medications, given MMP2's role as a target in cancer therapies. Through their interaction with essential residues, these compounds possess the ability to effectively inhibit MMP2 activity, a pivotal factor in the progression of cancer. As this is a computational study, it is essential to conduct experimental validation to confirm the therapeutic potential of these compounds. This will enable the development of these compounds into effective cancer treatments. Therefore, the research emphasizes the importance of these compounds as potential candidates for creating new therapeutic approaches that specifically target MMP2 in combating cancer.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, et al. Cancer statistics, 2004. CA: A Cancer Journal for Clinicians, (2004); 54(1): 8-29.
2. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell, (2010); 141(1): 52-67.
3. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nature Reviews Molecular Cell Biology, (2007); 8(3): 221-233.
4. Parks WC, Wilson CL, Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. Nature Reviews Immunology, (2004); 4(8): 617-629.
5. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovascular Research, (2006); 69(3): 562-573.
6. Roy R, Yang J, Moses MA. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. Journal of Clinical Oncology, (2009); 27(31): 5287-5297.
7. Liotta LA, Tryggvason K, Garbisa S, Hart I, Foltz CM, et al. Metastatic potential correlates with enzymatic degradation

of basement membrane collagen. Nature, (1980); 284(5751): 67-68.
8. Cauwe B, Van den Steen PE, Opdenakker G. The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Critical Reviews in Biochemistry and Molecular Biology, (2007); 42(3): 113-185.
9. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nature Reviews Cancer, (2002); 2(3): 161-174.
10. Tauro M, Lynch CC. Cutting to the Chase: How Matrix Metalloproteinase-2 Activity Controls Breast-Cancer-to-Bone Metastasis. Cancers (Basel), (2018); 10(6): 185.
11. Fu Z, Xu S, Xu Y, Ma J, Li J, et al. The expression of tumor-derived and stromal-derived matrix metalloproteinase 2 predicted prognosis of ovarian cancer. International Journal of Gynecological Cancer, (2015); 25(3): 356-362.
12. Shen W, Xi H, Wei B, Chen L. The prognostic role of matrix metalloproteinase 2 in gastric cancer: a systematic review with meta-analysis. Journal of Cancer Research and Clinical Oncology, (2014); 140(6): 1003-1009.
13. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: principles, applications and recent advances. Current Topics in Medicinal Chemistry, (2014); 14(16): 1923-1938.
14. Zhu H, Zhang Y, Li W, Huang N. A Comprehensive Survey of Prospective Structure-Based Virtual Screening for Early Drug Discovery in the Past Fifteen Years. International Journal of Molecular Sciences, (2022); 23(24): 15961.
15. Jang C, Yadav DK, Subedi L, Venkatesan R, Venkanna A, et al. Identification of novel acetylcholinesterase inhibitors designed by pharmacophore-based virtual screening, molecular docking and bioassay. Scientific Reports, (2018); 8(1): 14921.
16. Sharma V, Jaiswal PK, Kumar S, Mathur M, Swami AK, et al. Discovery of Aporphine Analogues as Potential Antiplatelet and Antioxidant Agents: Design, Synthesis, Structure-Activity Relationships, Biological Evaluations, and in silico Molecular Docking Studies. ChemMedChem, (2018); 13(17): 1817-1832.
17. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods in Molecular Biology, (2015); 1263: 243-250.
18. Reddy RA, Sai Varshini M, Kumar RS. Matrix Metalloproteinase-2 (MMP-2): As an Essential Factor in Cancer Progression. Recent Patents on Anti-Cancer Drug Discovery, (2023). doi: 10.2174/0115748928251754230922095544. Online ahead of print.
19. Chien MH, Lin CW, Cheng CW, Wen YC, Yang SF. Matrix metalloproteinase-2 as a target for head and neck cancer therapy. Expert Opinion on Therapeutic Targets, (2013); 17(2): 203-216.
20. Kamal MA, H MB, I JH, R SA, M SH, et al. Insights from the molecular docking analysis of EGFR antagonists. Bioinformation, (2023); 19(3): 260-265.
21. Sayed Murad HA, M MR, Alqahtani SM, B SR, Alghamdi S, et al. Molecular docking analysis of AGTR1 antagonists. Bioinformation, (2023); 19(3): 284-289.
22. Elaimi A, Hanadi MB, Almutairi A, Alniwaider RA, Abulkaliq MA, et al. Insights from the molecular docking analysis of GRP78 with natural compound inhibitors in the management of cancers. Bioinformation, (2023); 19(1): 39-42.
23. I JH, Alsharif FH, Aljadani M, Fahad Alabbas I, Faqihi MS, et al. Molecular docking analysis of KRAS inhibitors for cancer management. Bioinformation, (2023); 19(4): 411-416.
24. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice. Frontiers in Pharmacology, (2019); 10: 1614.
25. George BP, Chandran R, Abrahamse H. Role of Phytochemicals in Cancer Chemoprevention: Insights. Antioxidants (Basel), (2021); 10(9): 1455.