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Exploring the effects of phytochemicals on matrix metalloproteinases in cancer treatment: An in-silico investigation

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Abstract

Cancer is one of the deadliest diseases, causing more deaths annually and imposing a significant burden on global healthcare. Matrix metalloproteinases (MMPs) are zinc-dependent extracellular matrix-remodeling endopeptidases that break down nearly all constituents of the extracellular matrix, including cancer tissues. This study was conducted to determine the maximum inhibitory effect of phytochemicals on MMPs using molecular docking techniques. Docking studies were performed on four different types of matrix metalloproteins, namely MMP2, MMP7, MMP9, and MMP11, with ligands of phytochemicals such as Capsaicin, Eugenol, and Piperine. Among the ligands, the piperine compound was observed to give the best interaction among the other ligands, showing a binding energy of -7.94 kcal/mol for MMP7 and -10.16 kcal/mol for MMP11. Piperine phytochemicals can be used for further in vivo studies on anti-carcinogenic treatments.

Keywords: Piperine, matrix metalloproteinases, molecular docking, phytochemicals

Introduction

Matrix metalloproteinases (MMPs) are a group of endopeptidases that rely on zinc for their activity. They play a crucial role in the degradation and remodeling of the extracellular matrix (ECM) during various biological processes, such as organogenesis, angiogenesis, wound healing, cell proliferation, apoptosis, and cancer progression. MMPs are initially secreted in an inactive form known as zymogens, except for MP-11. Their activation occurs outside the cell, either through the action of other MMPs or serine proteases [14]. Degradation of the extracellular matrix by MMPs promotes tumor invasion [13]. Specifically, the role of MMPs in cancer development is influenced by various factors, such as the location, stage of the tumor, composition of the substrate, and localization of the enzymes [7]. Currently, 24 MMPs have been identified in vertebrates, with 23 found in humans [19].

Apoptosis is a physiological process of cell death that is a better and safer therapeutic candidate for eliminating cancer cells. To create novel and potent therapeutic agents that induce apoptosis in cancer cells, a thorough understanding of the mechanisms underlying the formation and dissemination of tumor cells is essential [5]. Several methods have been developed to induce apoptosis, including radiation, chemotherapy, checkpoint inhibitors [16], anti-cancer antibodies [18], and adoptive cell therapies. Tyrosine kinase activity, angiogenesis inhibition, and tumor vascularization are important therapeutic targets that induce apoptosis and stop cell metastasis. Thus, Tyrosine kinases, MMP, and vascular endothelial growth factor are significant targets for anti-cancer therapy [11].

In recent decades, phytochemicals found in fruits, vegetables, whole grains, spices, and tea have been hot topics in the field of chemoprevention because of their various inhibitory effects on cancer initiation, promotion, progression, and metastasis [1]. The primary hot ingredient in chili peppers, which are consumed as a spice in many cultures worldwide, is capsaicin, a homovanillic acid derivative.

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It has long been used medicinally, and more recent research has been conducted on it to determine its analgesic properties [16], antioxidant effects [9], anti-inflammatory effects [12], and anti-obesity effects. Piperine and eugenol, derived from black pepper and clove, respectively, are utilized for their broad properties, such as antioxidant, antimicrobial, and anti-inflammatory activities. They exhibit anti-cancer properties by blocking pathways involved in the proliferation, migration, and invasion of cancer cells [10]. This study was conducted to explore the anti-carcinogenic potential of selected phytochemicals through comprehensive in silico techniques targeting MMPs.

Materials and Methods

To ensure coverage of the binding site of the structure, AutoDock4.2 was used to convert both the receptor and ligand structures into the pdbqt file format. This format contains atomic charges, atom-type definitions, and topological information (rotatable bonds) in the case of ligands. The ligand-receptor complex generated nine conformations using AutoDock Vina in the docking simulations. These conformations were ranked according to their binding energies. The 25 target proteins and ligands were docked using iGEMDOCK (version 2.1). The genetic algorithm (GA) parameters that governed the docking process were 300 (population size), 70 (generations), and 3 (number of solutions). The identity of bond energies, including hydrogen bonds (Hb), van der Waals bonds (VdW), and electrostatic interactions between ligands and proteins, was noted. Using PyMol and the DiscoveryStudio Visualizer26, the final conformations were displayed.

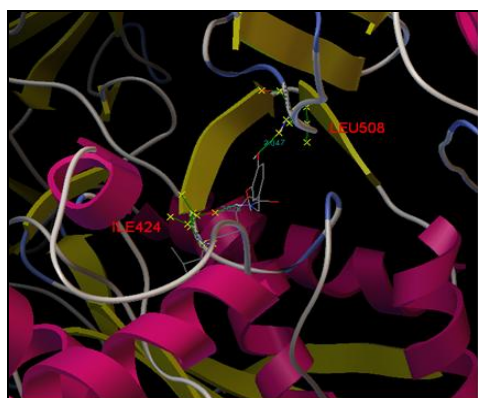


Fig 1: Interaction of MMP2 (1CK7) Protein with the ligand capsaicin. The interaction is observed at two sites, specifically LEU508 and ILE424

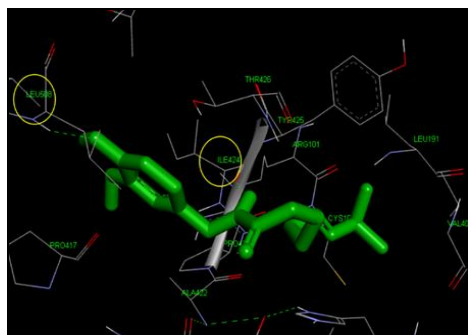


Fig 2: Interaction of MMP2 (1CK7) Protein with the ligand

Results and Discussion

Docking studies were performed on four different types of matrix metalloproteins (MMPs), namely MMP2, MMP7,

MMP9, and MMP11, with the ligands of Capsaicin, Eugenol, and Piperine phytochemicals.

- MMP2:** Docking results revealed that capsaicin showed the strongest binding affinity among the ligands, with a binding energy of -10.14 kcal/mol towards MMP2. Lower binding energies indicate favorable interactions that correlate with the greater stability of the ligand-phytochemical complex [8]. However, the interaction was observed at the level of LEU424 and LEU508, of which LEU508 was the residue that occurred in proximity but not within the active catalytic site of MMP2 (Figs 1 & 2). However, LEU508 was near S1, which is a critical substrate in the binding region. The non-active localization of capsaicin suggests that it may act as an allosteric modulator rather than an active site inhibitor. This can effectively regulate enzyme activity by triggering conformational changes that interfere with the catalytic efficiency of MMPs [4]. Eugenol showed a low binding energy of -6.89 kcal/mol at the ILE424 and THE426 regions, and piperine did not form any bonds with MMP2.
- MMP7:** The Piperine phytochemical had the highest binding affinity towards the MMP7 protein, with a binding energy of approximately -7.94 kcal/mol. It directly interacts with the residues (HIS218, HIS222, HIS228, and TYR240) of the active site of the protein, which increases the chances of competitive inhibition. The Piperine phytochemical directly interferes with the hydrolysis of the substrate. In epithelial cell tumors, MMP7 plays an important role in cell proliferation, progression, and the ability to induce other MMPs [17]. Capsaicin showed a binding energy of -7.97 kcal/mol and interacted with the catalytic histidines in MMP7 (ALA182, HIS228, and HIS218), indicating its potential for direct inhibition. Therefore, incorporating piperine into the treatment regimen will target MMP7 and reduce its activity by blocking the active site of the protein. Eugenol bound at the level of ALA182, ALA182, and LEU181 with a binding energy of -6.18 kcal/mol, which was weaker than that of the other compounds.
- MMP9:** Capsaicin formed three H-bonds with MMP9 at the level of ARG244, ARG244, and ALA235, with a binding energy of -9.96 kcal/mol, which was near the catalytic domain. Eugenol interacted with ARG249, located near the active site, with a binding energy of -6.86 kcal/mol. The piperine phytochemical showed the most favorable and strongest binding energy of -11.31 kcal/mol, which was the lowest among the other ligands tested. However, the binding occurred at the level of LEU188 and ALA189, which is outside the active site. ALA189 resided in the loop region, next to the S1' pocket, a critical subsite for substrate specificity in MMP9 [3], suggesting a non-competitive/peripheral mode of binding. Further studies, such as mutagenesis or dynamic simulations, are needed to confirm whether this allosteric binding induces functional modification.
- MMP11:** In the docking of ligands with the MMP11 protein, piperine showed the best interaction, with a binding energy of -10.16 kcal/mol. However, the interacting amino acids were not bound to the active site. The lack of active site engagement indicates a possible allosteric mechanism. This protein has not been studied as much as other MMPs, but it is involved in tumor immune evasion and stromal remodeling [2]. This allosteric effect on MMP11 is advantageous as it

minimizes off-target effects on other MMPs, which has been a major challenge in the development of broad-spectrum MMP inhibitors [6]. Capsaicin interacted and bound at the level of ARG244, ARG244, and ALA235 with a binding energy of -9.96 kcal/mol owing to its structural similarity with the MMP9 protein. Eugenol interacted with ALA235, ARG244, and ARG244, exhibiting a minimal binding energy of -7.89, compared to others.

Among the selected phytochemicals, piperine exhibited the strongest interactions and the highest binding affinity, particularly with MMP9 and MMP11, which demonstrated non-active-site binding. The flexible aromatic structure and its ability to engage in hydrophobic interactions with nonpolar residues on the enzyme surface provide a broad and stable interaction profile. Capsaicin can also be used as a broad-spectrum MMP inhibitor because of its effect on MMP9 and MMP11. Although Capsaicin and Eugenol showed some activity, their effects were less consistent across the target enzymes, further underscoring piperine as the most promising candidate for future studies.

Conclusion

In modern drug discovery, computational approaches, specifically in silico studies, such as molecular docking, molecular dynamics simulations, and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling, have emerged as powerful tools. Docking studies help predict binding affinities and assess drug-likeness, cost, and time effectiveness, thereby increasing the chances of identifying potential molecules. In this study, piperine exhibited the most favorable and consistent interactions with multiple MMPs. In MMP7, active site binding was demonstrated, indicating potential for competitive inhibition. Allosteric binding was observed for piperine with MMP9 and MMP11 and for capsaicin with MMP2. These findings support the ability of phytochemicals to act as MMP modulators in in silico models; however, experimental validation is essential to establish functional relevance.

Conflict of Interest: Not available

Financial Support: Not available

Reference

- Bergers G, Coussens LM. Contribution of the tumor microenvironment to cancer progression and metastasis. *Nat Rev Cancer*. 2007;7(1):59-72.
- Bertini I, Del Bianco C, Gelis I, Katsaros N, Luchinat C, Parigi G, *et al*. Experimentally exploring the conformational space sampled by domain reorientation in calmodulin. *Proc Natl Acad Sci, USA*. 2004;101(18):6841-6.
- Brew K, Nagase H. The tissue inhibitors of metalloproteinases (TIMPs): An ancient family with structural and functional diversity. *Biochim Biophys Acta*. 2010;1803(1):55-71.
- Chakravarti B, Maurya R, Siddiqui JA, Bid HK, Rajendran SM, Yadav PP, *et al*. In vitro anti-breast cancer activity of ethanolic extract of *Wrightia tomentosa*: Role of pro-apoptotic effects of oleanolic acid and urosolic acid. *J Ethnopharmacol*. 2012;142(1):72-79.
- Coussens LM, Fingleton B, Matrisian LM. Matrix metalloproteinase inhibitors and cancer: Trials and tribulations. *Science*. 2002;295(5564):2387-2392.
- Decock J, Hendrickx W, Vanleeuw U, Belle VV, Huffel VS, Christiaens MR, *et al*. Plasma MMP1 and MMP8 expression in breast cancer: Protective role of MMP8 against lymph node metastasis. *BMC Cancer*. 2008;8:1-8.
- Ferreira LBS, Nowroozadeh MH, Ghorat F. How significant are docking scores? *Curr Comput Aided Drug Des*. 2015;11(2):120-126.
- Galano A, Martínez A. Capsaicin, a tasty free radical scavenger: mechanism of action and kinetics. *J Phys Chem B*. 2012;116(3):1200-1208.
- Ghasemi M, Nowroozadeh MH, Ghorat F, Iraj A, Hashempour MH. Piperine and its nanoformulations: A mechanistic review of their anti-cancer activities. *Biomed Pharmacother*. 2025;187:118075.
- Iheagwam FN, Ogunlana OO, Ogunlana OE, Isewon I, Oyelade J. Potential anti-cancer flavonoids isolated from *Caesalpinia bonduc* young twigs and leaves: Molecular docking and in silico studies. *Bioinform Biol Insights*. 2019;13:1177932218821371.
- Kim CS, Kawada T, Kim BS, Han IS, Choe SY, Kurata T, *et al*. Capsaicin exhibits anti-inflammatory properties by inhibiting I κ B- α degradation in LPS-stimulated peritoneal macrophages. *Cell Signal*. 2003;15(3):299-306.
- Kohrmann A, Kammerer U, Kapp M, Dietl J, Anacker J. Expression of matrix metalloproteinases (MMPs) in primary human breast cancer and breast cancer cell lines: New findings and review of the literature. *BMC Cancer*. 2009;9(1):1-20.
- Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. *Cardiovasc Res*. 2006;69(3):562-73.
- Simeone E, Ascierto PA. Immunomodulating antibodies in the treatment of metastatic melanoma: The experience with anti-CTLA-4, anti-CD137, and anti-PD1. *J Immunotoxicol*. 2012;9(3):241-7.
- Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain*. 1989;38(1):99-107.
- Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol*. 2001;17(1):463-516.
- Sun J, Chia S. Adjuvant chemotherapy and HER-2-directed therapy for early-stage breast cancer in the elderly. *Br J Cancer*. 2017;116(1):4-9.
- Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF- β and promotes tumor invasion and angiogenesis. *Genes Dev*. 2000;14(2):163-176.

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