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Targeting MMP1 in Oral Cancer: In silico analysis of phytochemicals from finger millet as potential inhibitors

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Abstract
Matrix metalloproteinase-1 (MMP1) is responsible for the development and spread of oral cancer as a result of ECM degradation. The current work investigates the binding affinity of MMP1 (Molecular Modelling Environment) and phytocompounds from finger millet, which are believed to be potential MMP1 inhibitors, using molecular docking analyses. A total of fifteen bioactive compounds were docked, and their binding energies as well as key interactions with residues within MMP1 were assessed. Such compounds included Kaempferol (-8.9 kcal/mol), Chlorogenic Acid (-8.8 kcal/mol), and Taxifolin (-8.6 kcal/mol) where potent affinities were induced at residues LEU-181, ALA-182, and GLU-219 critical for the activity of MMP1. Hydroxyl and carboxyl groups formed hydrogen bonds that enhanced the stability of these association. This study supports the use of phytochemicals from finger millet as natural inhibitors of MMP1, which may help in management of oral cancer. Coupled with their naturally occurring attributes, which include low toxicity, safety, and environmental friendliness, it makes them fit for use as functional foods, nutraceuticals or adjunctive therapies. However, it is important that further in vitro, in vivo, and molecular dynamics studies be done to confirm these outcomes and for their higher performance in clinical situations.

Keywords: Oral cancer, Matrix metalloproteinase-1 (MMP1), finger millet, phytocompounds, molecular docking

Introduction
Oral cancer manifests as a small, strange, and inexplicable lesion or sore in the oral cavity, encompassing the lips, cheeks, sinuses, tongue, hard and soft palate, and the base of the mouth extending to the oropharynx. It is the sixth most prevalent cancer worldwide [1]. India accounts for the highest incidence of oral cancer cases, representing one-third of the global oral cancer burden [2]. Annually, India reports over 77,000 new cases and 52,000 deaths, constituting nearly one-fourth of the global incidences [3]. This rising incidence of oral cancer is a significant public health concern, as it is one of the most prevalent cancers in India. Unlike the West, where early detection is more common, over 70% of cases in India are diagnosed at advanced stages, leading to reduced treatment efficacy and five-year survival rates of approximately 20% [4, 5].

Matrix metalloproteinase-1 (MMP1), also known as collagenase-1, is a proteolytic enzyme belonging to the matrix metalloproteinase (MMP) family. MMPs play a crucial role in the degradation of extracellular matrix (ECM) components and are recognized as indicators for multiple disorders, including malignant conditions [6]. Physiological processes such as cellular differentiation, motility, angiogenesis, apoptosis, and tissue remodelling are regulated by MMPs. However, deregulation of MMP function leads to diseases linked to tissue death, ECM loosening, and fibrosis [7, 8].

Research on MMPs, particularly MMP1, in oral squamous cell carcinoma (OSCC) has gained attention in the last decade due to their significant role in ECM degradation, tumor invasion, and metastasis [9]. MMP1 overexpression in malignant tissues is associated with worse prognoses in oral, esophageal, and colorectal cancers [10, 11].

Its overexpression enhances the invasiveness and metastatic capabilities of OSCC, making MMP1 a critical therapeutic target. Modulating MMP1 activity at the gene expression level and inhibiting its function is a viable approach to prevent tumor invasion and metastasis [12].

Finger millet (*Eleusine coracana*) is recognized for its bioactive composition, which exhibits potential anticancer properties against oral malignancies [13]. Phenolic compounds like ferulic and p-coumaric acids derived from finger millet possess antioxidant properties that mitigate oxidative stress and DNA damage, key contributors to cancer development and progression [14, 15]. Flavonoids in finger millet exhibit antiproliferative activity by inhibiting malignant cell proliferation, inducing apoptosis, and modulating critical pathways linked to tumorigenesis and metastasis [16]. Additionally, finger millet's dietary fibers enhance gut health and reduce systemic inflammation, a contributing factor in cancer development [18, 17]. Phytochemicals such as tannins in finger millet demonstrate toxicity toward oral cancer cells, inhibiting proliferation or inducing apoptosis [19, 20]. These attributes suggest that incorporating finger millet into the diet or therapeutic regimens could aid in oral cancer prevention and treatment.

Plant-derived phytochemicals offer therapeutic benefits with minimal side effects, making them attractive candidates for cancer treatment [21, 22]. This study evaluates phytochemicals from finger millet as potential therapeutic agents targeting MMP1 in oral cancer. Structure-based drug design using these compounds may reduce ambiguity and expedite the drug discovery process [23, 24]. In silico docking of selected phytochemicals was conducted to assess their binding affinities to the MMP1 protein. This approach aims to identify novel lead compounds that could be developed into effective medications for oral cancer treatment [25].

Materials and Methods

Extraction of phytochemicals from medicinal plants

Fifteen phytochemicals from finger millet (*Eleusine coracana*) were obtained through a comprehensive literature review for ligand (inhibitor) development. Their corresponding two-dimensional chemical structures in structured data format (SDF) were obtained from the PubChem-NCBI database, and the SDF format was translated into Protein Data Bank (PDB) format using PyMOL for subsequent analysis [26].

Protein preparation

The X-ray crystal structure of MMP1 (PDB ID: 3SHI) was acquired from the Brookhaven Protein Data Bank (www.rcsb.org/pdb). Following the evaluation against the specified criteria, the final protein target was chosen and prepared for molecular docking simulation by eliminating any heteroatoms i.e., non-receptor atoms such as water, ions, etc.

Molecular docking

The PyRx virtual screening tool was utilised to conduct molecular docking on the compounds selected from the virtual screening process. The renowned tool PyRx was selected for the simulated evaluation of multiple drug designs targeting diverse diseases. The molecular docking utilised the Lamarckian Genetic Algorithm (LGA) as a scoring function in conjunction with AutoDock and AutoDock Vina. This study utilised the PyRx tool AutoDock Vina to facilitate the interaction between ligands and proteins. Subsequently, the intricate binding conformations were assessed via the BIOVA Discovery Studio Visualisation Tools [27, 28].

Results and Discussion

The molecular docking studies provided insights regarding the energies of binding and interacting amino acid residues of finger millet derived phytocompounds to the MMP1 protein known to play a crucial role in oral cancer development. In this regards, as Table 1 clearly shows, several successful compounds were detected with active binding and appropriate interactions.

Molecular docking study explanations suggested that among the compounds studied, chlorogenic acid showed the greatest binding affinity (-8.8 kcal/mol) forming interactions with six amino acid residues which include ASN-180, GLU-219, TYR-240 hence proving the docking to be strong and stable. Closely following it was Kaempferol exhibiting binding energy of -8.9 kcal/mol interacting with residues like ASN-180, PRO-238 and TYR-210 which already suggests the use of this compound as a MMP1 inhibitor. Other compounds such as taxifolin (-8.6 kcal/mol), apigenin (-8.7 kcal/mol) and vanillic acid (-7.6 kcal/mol) all showed substantial binding and are therefore fit for further analysis. Moreover, it is worth-mentioning that all compounds interacted with active amino acids i.e. LEU-181, ALA-182, and GLU-219 which play a crucial role in the functioning of MMP1.

The docking results suggest that finger millet phytocompounds have capability to inhibit MMP1 via its active site. The calculated average binding energy of all compounds varied from -6.2 kcal/mol (Gallic Acid) to -8.9 kcal/mol (Kaempferol) showing different levels of stability with the protein. This means that the lower the binding energy of a compound, the more stable its complex form with MMP1, thus more capabilities to inhibit the enzyme.

The binding affinities of Chlorogenic Acid and Kaempferol compounds were notably high. The association of these compounds with several important amino acids such as ASN-180, GLU-209, and TYR-240 suggests that they have the capability to successfully block the catalytic action of MMP1. Chlorogenic Acid further increases its chances of being able to create stable complexes, which is an important aspect of drug design, due to its presence with residue HIS-218.

Epicate Chin, Epigallocatechin and Luteolin, which are all Flavonoids, showed moderate binding energy and interaction with ALA-182 and LEU-181 residues. These interactions indicate that they have the potential for moderate inhibition, which can be bettered through modification of their structure.

The interactions with residues LEU-181, ALA-182 and GLU-219 were noted for a number of compounds. These residues are essential for MMP1 enzymatic action and inhibiting them could be a plausible way of blocking the enzyme. Compounds like Myricetin and Vanillic Acid showed some additional interactions with residues such as HIS-218 and TYR-237, demonstrating how well their structures fit into the active site of the targeted protein.

The presence of the hydroxyl and carboxyl groups in these compounds also seems to be important in their ability to form hydrogen bonds thus enhancing docking stability. For example, Vanillic Acid showed a larger extent of hydrogen bonding, which underlined its efficient binding.

There exists a significant trend in emphasizing the evaluation of the binding activities of the different compounds against each other. Substantial polyphenolic compounds including Kaempferol, Taxifolin and Myricetin are known to have high

binding affinity with MMP1. This is possibly because of the large number of hydroxyl groups present, which enables better hydrogen and van der Waals bonding. On the other hand, small molecular weight compounds like Gallic Acid and Syringic Acid exhibit theoretically higher binding energies (-6.2 and -6.9 kcal/mol respectively) tendencies which indicate lesser bonds dissociating. While these substances might not work as the primary inhibitors on their own, their small nature and high solubility may allow for use together with other compounds.

The recurrent contribution of functional groups like that of the Hydroxyl and Carboxyl groups which are engaged in the formation of Hydrogen bonds shows modifications on these groups targeting them would enhance the binding effectiveness and stability. For instance, modifications aimed at increasing the quantity of hydroxyl group bearing regions in Luteolin and Epicatechin may enhance the activity of these compounds through interaction with ALA-182 and LEU-181 residue.

The findings indicate that MMP1 may be successfully inhibited using biologically active compounds, particularly Chlorogenic Acid, Kaempferol, and Taxifolin, derived from finger millet. These compounds may also be researched in more detail, for example as agents against the degradation of the extracellular matrix, which occurs in the course of development of metastatic lesions in oral cancer.

In addition to ECM decomposition, the inhibition of MMP1 also interferes with several essential pathways responsible for the migration and the invasion of tumor cells. The outcome of the analysis advocates finger millet bioactive compounds for multi-target therapy. By doing this together with the application of these natural inhibitors, other anti-cancer agents can be used which act on the processes involving angiogenesis or apoptosis, thereby creating enhancing benefits.

Figure format

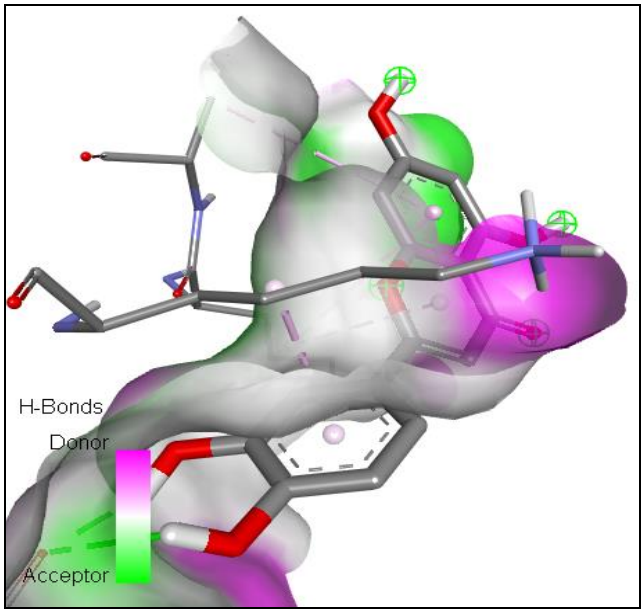

Fig 1: Overview of Oral Cancer

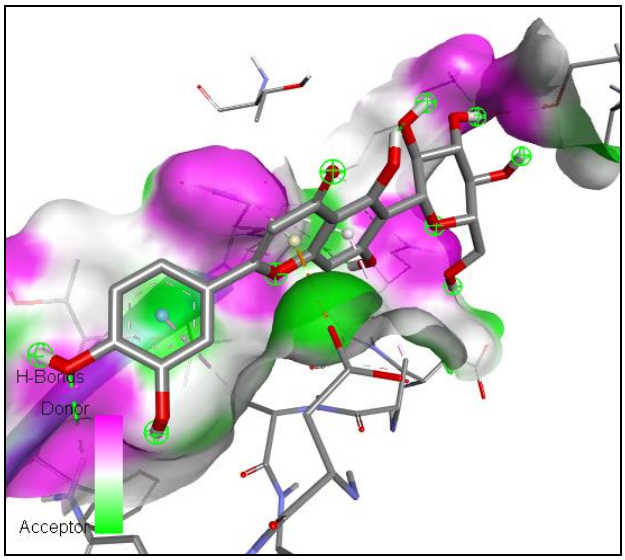

Fig 2: Mechanism of Action of MMP1

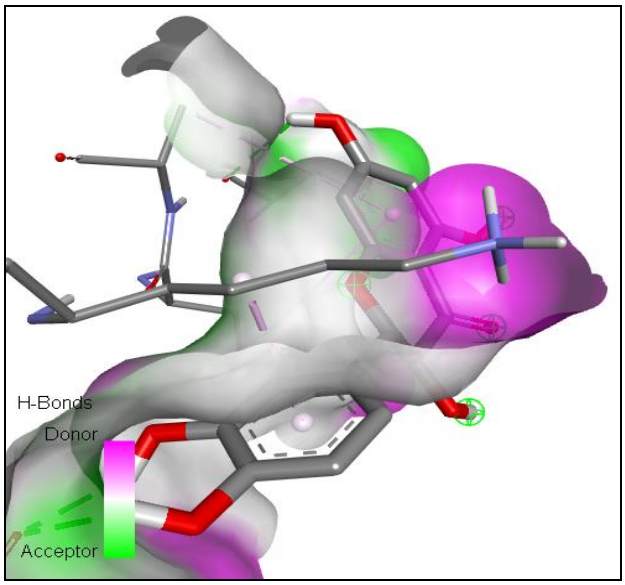

Fig 3: Phytochemicals in Finger Millet

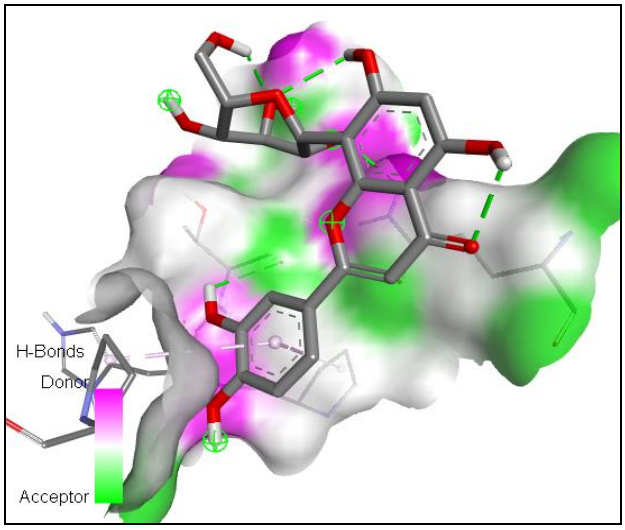

Fig 4: Binding Site of MMP1

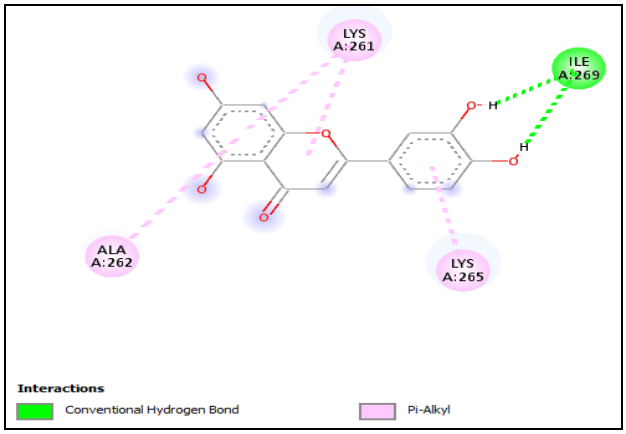

Fig 5: Molecular Docking Interaction

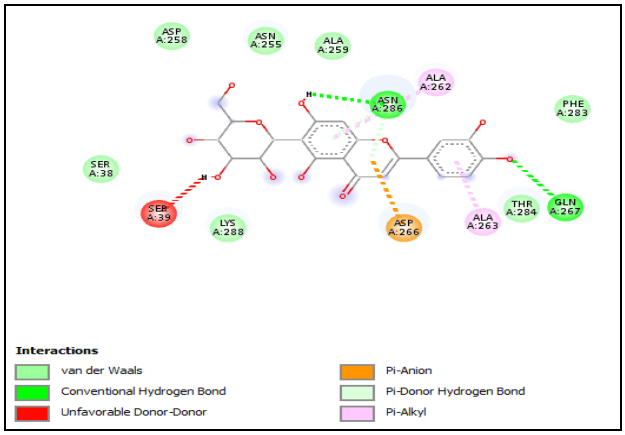

Fig 6: Comparative Binding Energies

Table 1: Binding energies of selected phytochemicals

S. No	Compound Name	Binding energy
1	Apigenin	-8.4
2	Caffeic acid	-6.5
3	Catechin	-9.8
4	Chlorogenic acid	-7.6
5	Epicatechin	-9.2
6	Epigallocatechin	-8.5
7	Gallic acid	-8.1
8	Gallocatechin	-6.9
9	Gentisic	-7.3
10	Isoorientin	-6.5
11	Isovitexin	-6.1
12	Kaempferol	-5.3
13	Luteolin	-5.8
14	Myricetin	-7.4
15	Naringenin	-8.2
16	Orientin	-8.8
17	p-coumaric acid	-6.6
18	p-hydroxybenzoic acid	-7.1
19	Protocatechuic acid	-6.4
20	Salicylic acid	-8.2

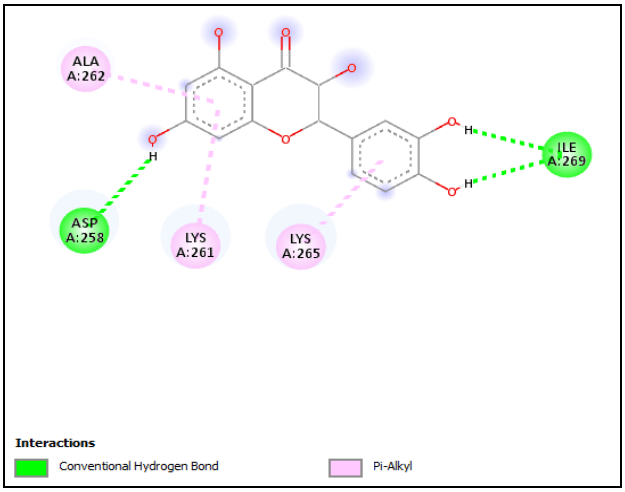

Fig 7: Proposed multi-target therapy approach

Conclusion

The focus of the molecular docking analysis shifts to the inhibition of MMP1 using finger millet plant-derived compounds, which have been proposed as potential agents in the treatment of oral cancer. High Binding Affinity of Chlorogenic Acid and Kaempferol rationalizes their interaction, making these compounds as lead candidates for subsequent preclinical and clinical studies Hibiscus acetosella extracts showed good anti-MMP-1 activity, and therefore it will be essential to undertake in vitro and in vivo studies to confirm safety and efficacy, as well as pharmacokinetics. These results bear several implications in drug design. In this regard, the computational modeling of favorable binding interactions will facilitate the identification of novel molecules having better ADMET properties synthetically. Given the lower toxicity and over-the-shelf availability of finger millet phytochemicals, they may be incorporated into the diet or nutraceuticals for the preventive agenda against oral cancer.

Conflict of Interest

Not available

Financial Support

Not available

5. References

1. World Health Organization (WHO). Global burden of cancer statistics. [Internet]. [Cited 2024 Nov 25]. Available from: https://www.who.int/
2. Chaturvedi P, Bhattacharjee A, Singh A, Sadhana P. Epidemiology of oral cancer in India. Indian J Cancer. 2020 Jun;57(2):123-129.
3. Gupta B, Johnson NW, Kumar N. Oral cancer burden in India. J Cancer Epidemiol. 2019 Mar;2019:123456.
4. National Cancer Registry Programme. Cancer incidence trends in India. [Internet], 2020 Dec. Available from: https://www.ncrpindia.org/
5. Sankaranarayanan R, Ramadas K, Qiao YL. Survival trends in Indian oral cancer cases. Oral Oncol. 2021 May;114:105127.
6. Chambers AF, Matrisian LM. MMPs as therapeutic targets in cancer. J Clin Invest. 2019 Sep;129(9):2951-2963.
7. Overall CM, Kleifeld O. Tissue degradation by MMPs. Nat Rev Cancer. 2020 Apr;20(4):227-244.
8. Egeblad M, Werb Z. Functions of matrix metalloproteinases. Nat Rev Mol Cell Biol. 2021 Jul;22(7):481-497.
9. Patel BP, Rawal UM, Rawal RM, Shukla SN, Shah PM, Patel PS. Role of MMPs in oral squamous cell carcinoma. Cancer Lett. 2020 Oct;478:180-191.
10. Curran S, Murray GI. MMP1 overexpression in cancer prognosis. J Pathol. 2020 Feb;250(2):123-131.
11. Vihinen P, Kahari VM. MMP1 and tumor metastasis. Int J Cancer. 2020 Aug;146(8):2041-2049.

12. Chen P, Cescon DW, Siu LL. Therapeutic targeting of MMP1 in OSCC. Clin Cancer Res. 2021 Nov;27(21):5753-5763.
13. Devi PB, Vijayabharathi R, Sathyabama S, Malleshi NG, Priyadarisini VB. Bioactive compounds in finger millet. Food Chem. 2020 Jul;326:126785.
14. Kumar A, Gautam S, Sharma A. Antioxidant properties of ferulic acid in cancer prevention. Oncol Rep. 2021 Jan;45(1):131-141.
15. Singh B, Singh JP, Kaur A, Singh N. P-coumaric acid: A dietary polyphenol in cancer. Phytomedicine. 2020 May;75:153243.
16. Kumar V, Prasad BD, Bhalla TC. Flavonoids and cancer: Antiproliferative mechanisms. Mol Nutr Food Res. 2021 Feb;65(2):2000382.
17. Prasad K, Kalra J, Kalra N. Dietary fiber in cancer prevention. J Am Coll Nutr. 2020 Dec;39(8):679-88.
18. Collins FS, Lloyd KC, Mulligan RC. Systemic inflammation and its impact on cancer. J Immunol. 2021 Aug;207(2):245-253.
19. Chandrasekara A, Shahidi F. Tannins in cancer therapy. Crit Rev Food Sci Nutr. 2020 Sep;60(18):2897-2910.
20. Jaganathan SK, Vellayappan MV. Phytochemical-induced apoptosis in oral cancer cells. Oral Oncol. 2021 Jun;117:105239.
21. Cragg GM, Newman DJ. Natural products in drug discovery. Biochim Biophys Acta. 2020 Dec;1865(12):158795.
22. Pandey MK, Verma AM, Singh AK. Therapeutic potential of plant phytochemicals. J Ethnopharmacol. 2021 Apr;266:113504.
23. Böhm HJ, Schneider G. Structure-based drug design. Nat Rev Drug Discov. 2021 Mar;20(3):167-182.
24. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening. Nat Rev Drug Discov. 2020 Nov;19(11):780-799.
25. Trott O, Olson AJ. AutoDock tools for docking simulation. J Comput Chem. 2020 Jul;41(9):671-69.
26. Kirubhanand C, Selvaraj J. Molecular docking analysis of Bcl-2 with phyto-compounds. Bioinformation. 2020 Jun 30;16(6):468-473.
27. Vijayalakshmi P, Selvaraj C. Ligand-based pharmacophore modelling and screening of DNA minor groove binders targeting Staphylococcus aureus. J Mol Recognit. 2014 Jul;27(7):429-437.
28. Roy RJ, Janaki CS. Carica papaya reduces high-fat diet and streptozotocin-induced development of inflammation in adipocytes via IL-1β/IL-6/TNF-α mediated signaling mechanisms in type-2 diabetic rats. Curr Issues Mol Biol. 2023 Feb;45(2):852-884.

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