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Natural Terpenoids as Potential MMP-7 Inhibitors in Colon Cancer: A Computational Screening Study

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ABSTRACT

Background: Colorectal cancer is the third most frequent cancer globally. Incidence rises with age and has been highest in developed countries, but it is rapidly increasing in many less developed countries and among younger generations in both developed and developing nations. MMP-7 is a key enzyme in the progression of colon cancer, making it a potential therapeutic target.

Methods: This study used a computational screening method to determine the efficacy of natural terpenoids as MMP-7 inhibitors. The MMP-7 inhibitor TQI was used as a positive control. A total of 355 natural terpenoid compounds were gathered from literature and public databases. Each compound was obtained in SDF format, converted into 3D structures for molecular docking analyses. PyRx (0.8 version), utilizing the AutoDock Vina docking engine was employed for virtual screening through molecular docking.

Results: Three potential candidates, retinol (vitamin A), carnosic acid, and gibberellic acid, were identified as showing strong binding affinities toward MMP-7 compared with the co- crystallized inhibitor TQI. ADMET analysis indicated compound- specific pharmacokinetic and safety profiles: retinol exhibited high predicted oral bioavailability but lower solubility, whereas carnosic acid and gibberellic acid showed more favorable non- toxicity and hERG safety percentiles.

Conclusion: These findings highlight the promise of natural terpenoids as novel MMP-7 inhibitors in colon cancer treatment, necessitating further validation and experimental research to determine their efficacy and therapeutic potential.

INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide in terms of overall cancer incidence. The global incidence of colorectal cancer was ~1.9 million in 2020 and is projected to reach over 3 million by 2040, with high morbidity and mortality rates [1,2]. The etiology of colon cancer is defined by unique genetic instability that contributes to uncontrolled cell growth and metastasis of malignant cells [3].

Matrix metalloproteinases (MMPs) promote cancer growth by damaging the ECM, allowing tumor invasion and metastasis. These enzymes promote cancer cell motility, immunological evasion, and resistance to apoptosis, making them important indicators and potential therapeutic targets [4]. MMP-7 has been associated with colon cancer within the MMP family. It is overexpressed in colorectal tumor and contributes to the degradation of key ECM components such as laminin and fibronectin, which promotes tumor development [5].

MMP-7 promotes tumor microenvironment remodelling by activating more MMPs and cleaving cell adhesion molecules such as E- cadherin, hence increasing epithelial- to- mesenchymal transition and metastatic potential [6,7]. Its role in regulating inflammation and signalling pathways, including Wnt/ β- catenin, highlights its importance in the etiology of colon cancer [8,9].

Natural compounds have made a substantial contribution to pharmacotherapy. Their various chemical structures have evolved to successfully interact with biological macromolecules, making them major resources for medication development [10,11]. Terpenoids, a class of secondary metabolites produced from isoprene units, demonstrate a variety of pharmacological activities, including anticancer, anti-inflammatory, and antimalarial actions [12]. These bioactive chemicals have a tremendous therapeutic promise, particularly for cancer therapy [13,14]. This study aimed to find natural MMP-7 inhibitors to manage cancer.

METHODS

MMP-7 3D structure retrieval and preparation

3D MMP-7 structure (PDB ID: 2Y6C, 1.68 Å) was obtained from the PDB database [15,16]. To prepare the molecular docking structure, co- crystallized water molecules not engaged in significant interactions were eliminated. The zinc ion and its coordinating residues were retained to maintain the integrity of the enzyme's active site. The co- crystallized inhibitor TQI (PubChem ID: 2109230) was also retrieved to use as a reference compound. Structural refinements and visualization were conducted using Discovery Studio Visualizer 2021, and the purified protein structure was transformed into PDBQT format with PyRx for subsequent virtual screening experiments [17].

Terpenoid compounds library preparation

The MMP-7 inhibitor TQI was obtained in SDF format from the PubChem database, energy-minimized, and used as a positive control in the study. A total of 355 natural terpenoid compounds were gathered from the Selleckchem database (http:// seo.selleckchem.com/ screening/ natural- terpenoid- compound- library.html). Each compound was obtained in SDF format, converted to 3D structures, and energy-minimized using PyRx's Universal Force Field to ensure optimal conformations for molecular docking analyses.

Virtual screening

PyRx (version 0.8) with the AutoDock Vina docking engine [18] was used for virtual screening. A receptor grid was established, centered on the catalytic zinc ion and its neighboring pocket residues, to guarantee comprehensive coverage of the active site. The co- crystallized inhibitor TQI was re- docked using the same grid and Vina settings applied for ligand screening, producing a heavy- atom RMSD of 1.5 Å, confirming reproducibility of the native pose. All terpenoid compounds were docked flexibly, allowing conformational adjustments to enhance binding interactions. The docking outcomes were assessed using binding free energy (kcal/ mol), and the highest-ranked candidates were selected based on their lowest binding energies. Ultimately, 2D and 3D visualizations of the docking interactions were generated using Discovery

Studio Visualizer for enhanced structural analysis.

ADMET predictions

The ADMET properties of the identified terpenoid compounds have been predicted utilizing the ADMET-AI web tool (https:// admet.ai.greenstonebio.com). This tool employs machine learning models trained on comprehensive datasets sourced from the Therapeutics Data Commons to deliver swift, reliable predictions of pharmacokinetic and toxicological parameters [19].

RESULTS

This study employed *in silico* techniques to identify novel natural MMP-7 inhibitors from a varied library of natural terpenoids. The justification for focusing on MMP-7 in colon cancer arises from its essential function in ECM degradation, facilitating tumor invasion and metastasis.

The prepared MMP-7 protein structure, the selected terpenoid compounds, and the control inhibitor (TQI) were subjected to virtual screening using PyRx. The docking grid was established utilizing XYZ coordinates (−8.8, −18.1, −7.7) to guarantee optimal coverage of the active site. Docking results showed that retinol (vitamin A), carnosic acid, and gibberellic acid had the strongest binding affinities, with docking scores of -8.3 kcal/ mol, -8.2 kcal/ mol, and -8.2 kcal/ mol, respectively (Table 1). The values obtained were significantly stronger than those of the established MMP-7 inhibitor TQI, which had a docking score of -7.4 kcal/ mol. The re-docked crystallographic control (TQI) reproduced the experimental binding orientation with a heavy-atom RMSD of 1.5 Å, validating the reliability of the scoring environment used for affinity comparison.

The docking poses were analysed using Discovery Studio, indicating that these three compounds exhibited the most stable interactions within the MMP-7 binding pocket (Figure 1). The analyses of 3D and 2D interactions (Figure 1) confirmed the stable binding of the leading compounds within the MMP-7 active site. Interactions with critical residues, such as His229, Tyr172, and Pro104, indicate their possible roles as inhibitors. Retinol exhibited the strongest binding affinity, while carnosic acid and gibberellic acid showed similar binding energies.

The 2D interaction analysis (Figure 2) confirmed stable binding within the catalytic pocket, characterized by strong hydrogen bonding and hydrophobic interactions with key enzymatic residues. In contrast to conventional MMP inhibitors that depend on zinc-chelating groups, these terpenoid scaffolds demonstrated advantageous interactions through alternative binding motifs, enhancing their therapeutic potential. Specifically, carnosic acid formed hydrogen bonds and hydrophobic interactions with Ala184, Phe103, and His183. Gibberellic acid interacted with critical active-site residues, such as Tyr172 and Thr180, suggesting its potential as an inhibitor. Retinol, the ligand with the highest affinity, demonstrated extensive interactions with Pro104, Phe103, and Ala186, indicating a notably strong binding mode. Compared to the control, these terpenoid compounds exhibit a tighter fit within the active site, enhancing their potential as natural MMP-7 inhibitors.

Finally, the ADMET analysis of the three hit candidates demonstrated unique pharmacokinetic and toxicological characteristics (Figure 3).

Figure 3 summarizes the ADMET-AI-predicted pharmacokinetic and safety profiles of retinol, carnosic acid, and gibberellic acid. Retinol showed high percentile values for predicted oral bioavailability but comparatively lower solubility, indicating that it is likely to be well absorbed yet formulation strategies may be needed to overcome solubility limitations. Carnosic acid exhibited moderate bioavailability with similarly low solubility but a more favorable non-toxicity profile. Gibberellic acid demonstrated relatively higher solubility and hERG safety percentiles compared with the other compounds. Overall, these radar plots highlight compound-specific ADMET strengths and limitations, which are further elaborated in the Discussion.

Figures

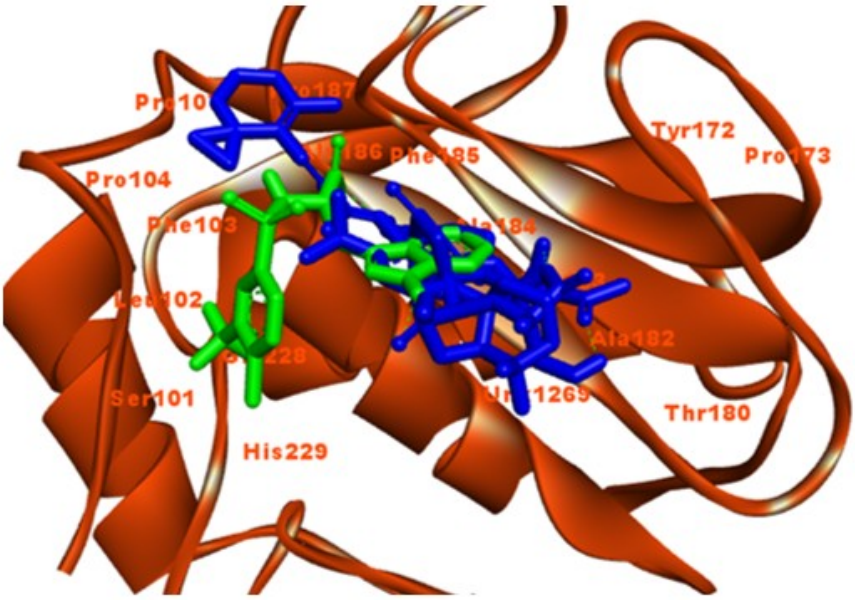

Figure 1: Interaction visualization of the top three terpenoid compounds, retinol, carnosic acid, and gibberellic acid (blue) docked within the active site of MMP-7, along with the control molecule (green).

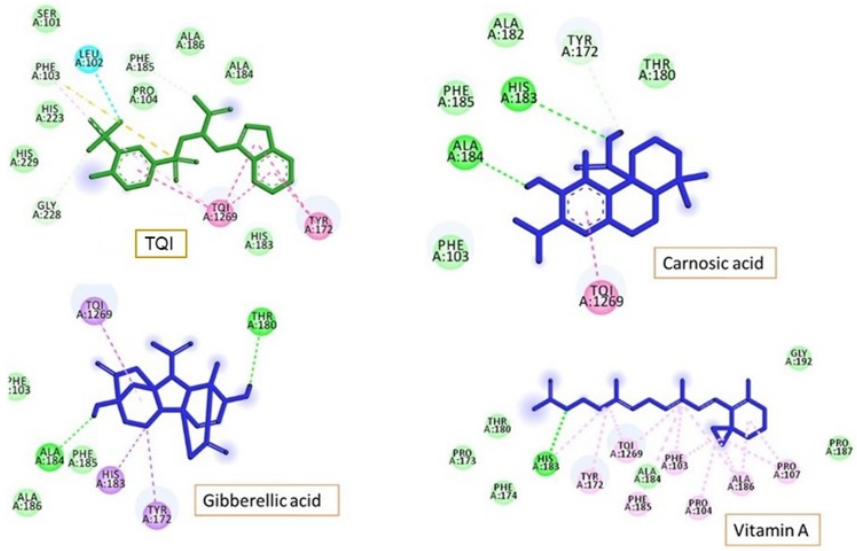

Figure 2: 2D interaction diagrams of the top three terpenoid compounds carnosic acid, gibberellic acid, retinol, and the control molecule within the MMP-7 active site. Carnosic acid, gibberellic acid, and retinol are shown in blue color stick representation, while the control molecule (TQI) is shown in green color stick representation.

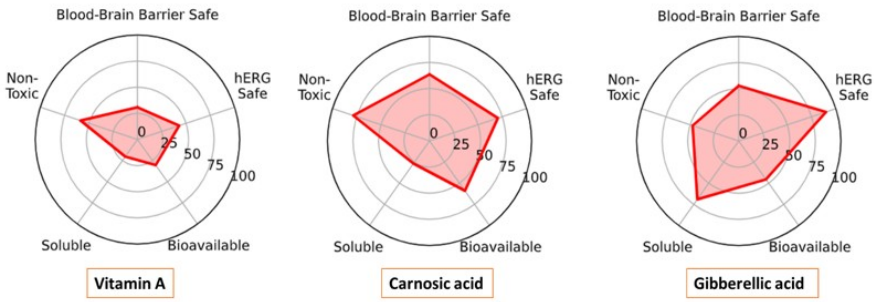

Figure 3. ADMET radar plots of retinol, carnosic acid, and gibberellic acid. The plots show normalized 0–100 percentile scores, with higher values indicating more favorable predicted pharmacokinetic or safety properties

for each endpoint (bioavailability, solubility, BBB safety, hERG inhibition safety, and non-toxicity). Percentile values denote relative rankings derived from ADMET-AI and do not directly represent absolute in vivo measures.

Tables

S. No.	Terpenoid compounds	Binding affinity (kcal/mol)
1.	Retinol (Vitamin A)	-8.3
2.	Carnosic acid	-8.2
3.	Gibberellic acid	-8.2
4.	Cephalomannine	-7.8
5.	Oleanolic Acid	-7.7
6.	Gamma Oryzanol	-7.7
7.	Asiatic acid	-7.6
8.	Limonin	-7.5
9.	Artemether	-7.4
10.	Sclareolide	-7.4
11.	TQI (positive control)	-7.4

Table 1: Top 10 selected terpenoids and their respective binding affinities with the MMP-7 protein.

DISCUSSION

Colon cancer is among the most frequent malignancies in the world. MMP-7 is a low-molecular-weight zinc- and calcium- dependent endopeptidase. It can degrade a wide range of ECM substrates and other substrates, as well as playing critical regulatory functions in many human pathophysiological processes. Since its discovery, MMP-7 has been identified as a regulatory protein involved in wound healing, bone formation, and remodelling. Later, MMP-7 was found to govern cancer incidence and progression, as well as mediate the growth, metastasis, and invasion of several cancer cell types [20]. This study uses *in silico* tools to find natural MMP-7 inhibitors from natural terpenoids. retinol, carnosic acid, and gibberellic acid had the strongest binding affinities to MMP-7.

This study screened the natural terpenoids against MMP-7. Retinol, carnosic acid, and gibberellic acid had the strongest binding affinities with the MMP-7. The interaction analysis revealed that MMP-7's catalytic pocket promotes binding through hydrogen bonding and hydrophobic interactions with critical amino acid residues. These compounds may be employed as natural MMP-7 inhibitors in cancer treatment. Additional validation studies are needed to establish their inhibitory activity and assess their potential as MMP-7 inhibitors.

High negative binding affinity values indicate a strong interaction between the ligand and the protein complex [21– 22]. Docking results revealed that retinol, carnosic acid, and gibberellic acid bind to MMP-7 more strongly than the control, suggesting a plausible protein- ligand interaction.

In interpreting the ADMET profiles (Figure 3), retinol (vitamin A) exhibited high predicted oral bioavailability but lower solubility, suggesting that while absorption may be efficient, its aqueous solubility could limit formulation and systemic exposure. In contrast, carnosic acid showed a more favorable non- toxicity profile but similarly limited solubility, and gibberellic acid demonstrated comparatively higher predicted solubility and hERG safety. These computational predictions indicate that retinol and carnosic acid may require formulation or structural

optimization to address solubility constraints, whereas gibberellic acid appears more balanced in terms of solubility and cardiac safety. Overall, carnosic acid and gibberellic acid exhibit safer ADMET profiles than retinol with respect to non-toxicity, but all three compounds warrant further experimental evaluation to confirm their safety and efficacy within the context of MMP-7-driven tumor biology.

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The author declare that Generative AI tools were used to enhance the language clarity of this work.

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