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In Silico Assessment of Demethoxycurcumin: Molecular Docking and Computational Insights into Its Various Therapeutic Potential

Prosenjit Dutta[1,*], Lata Khani Bisht[2], Vineeth Chandy[3]

Abstract

Natural compounds are increasingly explored for their therapeutic potential in medical research. Here, we focused on demethoxycurcumin (DMC), a polyphenolic bioactive compound extracted from Curcuma longa, commonly found in turmeric. DMC, with a chemical formula of C20H18O5 and a molecular weight of 340 g/mol, possesses two aromatic ring systems, each featuring a β-diketone moiety connected by a seven-carbon chain. This unique structure allows DMC to engage in tautomerism, which is crucial for their biological effects and interactions with specific molecular targets. We investigated the potential of demethoxycurcumin for the treatment of cancer, Alzheimer's disease, inflammation, and COVID-19 SARS Omicron variant infection using molecular docking and computational techniques. The methodology involves utilizing PubChem and PDB databases to obtain DMC's 3D structure of DMC and the crystal structures of the target proteins. Tools such as AutoDock 4.2 was employed to carry out molecular docking, Avogadro and BIOVIA Discovery Studio Visualizer was used for ligand and protein preparations, and ChimeraX was employed to visualize the molecular simulations. Molecular docking results exhibit promising affinities against cancer and Alzheimer's, with robust binding to inflammation-related proteins, indicating anti-inflammatory potential. Furthermore, the propensity of DMC to bind to SARS-CoV-2 Omicron variant proteins suggests its potential antiviral activity against COVID-19. Through molecular docking, we scrutinized DMC's interactions of DMC with disease-associated targets and highlighted its distinct properties as a compelling natural compound for diverse drug development avenues. The insights gained lay the groundwork for future studies, delving into the medicinal chemistry of demethoxycurcumin and identifying its potential as a multi-targeted therapeutic agent. As drug discovery advances, this research offers crucial information for innovative therapeutic development across challenging diseases.

Keywords: Demethoxycurcumin, cancer, Alzheimer's disease, inflammatory disorders, SARS-CoV-2 Omicron variant, molecular docking

***Author for Correspondence**
Prosenjit Dutta
E-mail: prosenjitdutta771@gmail.com

[1]Research Scholar, Department of Pharmacy, T John College of Pharmacy, Bengaluru, Karnataka, India
[2]Associate Professor, Department of Pharmaceutical Science, T John College of Pharmacy, Bengaluru, Karnataka, India
[3]Principal, T John College of Pharmacy, Bengaluru, Karnataka, India

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INTRODUCTION

Natural products are colossal reservoirs of biologically active compounds. In most cases, they have great therapeutic potential with minimal side effects. Turmeric and curcumin have long been recognized for their pharmacological effects, including anti-proliferative, anti-inflammatory, anti-cancer, antidiuretic, hypocholesterolemic, antithrombotic, antihepatotoxic, anti-diarrheal, carminative, diuretic, antirheumatic, antimicrobial, anti-virulent-oxidant, hypertensive, larvicidal, insecticidal, antivenomous, etc. [1]. In Asian countries, *Curcuma longa* is used as a medicinal herb and colorant in food, beverages, cosmetics, and nutraceuticals alone, or in conjunction with a plethora of other substances.

Turmeric contains polyphenols such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which give it a yellow color. Demethoxycurcumin (DMC) is a modified form of curcumin that lacks two methoxy groups on its phenolic ring. This alteration results in unique pharmacological properties that distinguish DMC from curcumin and other curcuminoids.

It shows good tolerability and safety profiles in clinical trials at doses between 4000 and 8000 mg/day, and even up to 12,000 mg/day (95% concentration) of three major curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin [2]. The challenge lies in low oral bioavailability due to its limited solubility in water at neutral or acidic pH and its instability in alkaline solutions. In addition, cellular efflux by P-glycoprotein and its rapid clearance from the body further complicate its therapeutic potential.

Curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, have garnered considerable attention because of their remarkable health benefits attributed to their potent antioxidant [3–4] and anti-inflammatory properties [5–7].

Over the past six decades, an array of studies has revealed curcumin's efficacy in treating diverse ailments such as cancer [8–9], type 2 diabetes [10–11], neurodegenerative diseases [12–13], cardiovascular disease [14], metabolic disorders [15], arthritis [16], autoimmune diseases [17], pulmonary disorders [18], and thrombotic disorders [19], and studies have shown promising antitumor effects of DMC, which may even surpass those of curcumin [20].

In this study, we explored the therapeutic efficacy and ADME properties of DMC by molecular docking with several critical proteins and receptors involved in cancer, Alzheimer's disease, anti-inflammation, and the COVID-19 SARS-2 (Severe Acute Respiratory) omicron variant.

MATERIALS

The 3D structure of DMC was obtained from the PubChem database, and the crystal structures of all target proteins were obtained from the PDB database and software used: AutoDock 4.2, Avogadro, BIOVIA Discovery Studio Visualizer, and ChimeraX (Figure 1).

METHODOLOGY

Protein and Ligand Preparations

The ligand was prepared using Avogadro software by optimizing the geometry, adding hydrogen atoms, assigning partial charges, and saving it in PDB format for docking. Protein structures were processed, irrelevant components were removed, and hydrogen atoms were added. Missing residues were addressed using homology modeling of the Swiss Model. Model validation was performed using the UCLA-DOE server and confirmed using RAMPAGE, ERRAT, and Verify3D online tools (Table 1).

The Active Site Prediction

Active site prediction was conducted for each target protein using the CAST-P online tool for ligand-binding site prediction. The most suitable active site for docking analysis was selected based on the ranking of the pocket with the largest volume.

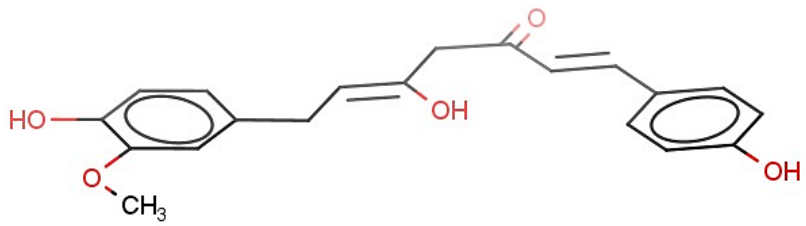

Figure 1. Chemical structure of demethoxycurcumin (DMC) drawn in MarvinSketch.

Table 1. Molecular docking results to determine the target receptors binding pocket affinity to DMC at 298.15 K.

Protein-ligand complexes	Binding energy (kcal/mol)	Final intermolecular energy (kcal/mol)	Inhibition constant (Ki)	RMSD (Å)	No. of hydrogen bonds
Cancer receptor-DMC	-9.46	-11.14	116.59 nM	120.078	1
Alzheimer's disease receptor-DMC	-8.06	-10.03	1.24 uM	77.792	3
Anti-inflammatory receptor-DMC	-10.35	-12.10	26.08 nM	68.966	3
SARS-CoV-2 receptor-DMC	-9.30	-11.09	151.88 nM	334.741	4

Docking

AutoDock 4.2 [21] was used for docking simulations between a rigid protein and a flexible ligand, following standard procedures. The active site of the protein was defined using a grid box with coordinates based on the site prediction results of the CAST P tool. The grid spacing is 0.5 Å using AutoGrid. Electrostatic mapping uses the distance-dependent dielectric constant. Docking employed the Lamarckian Genetic Algorithm (LGA) [22] with an initial population of 150 individuals and up to 2,500,000 energy evaluations per run. More than 20 runs were performed for each receptor to ensure reliability.

Binding Modes Analysis

After the completion of docking simulations, the best binding conformations were analyzed using powerful software tools such as ChimeraX [23].

ADME PROPERTIES PREDICTIONS

The SwissADME [24] platform was employed to predict various ADME properties of demethoxycurcumin, such as lipophilicity (logP), water solubility, oral bioavailability, distribution potential, metabolic site prediction, and GI absorption.

RESULTS AND DISCUSSIONS

Cancer—Dihydrofolate Reductase (DHFR) (PDB ID: 1AO8)

The leading docking cluster displayed a stable structure with an RMSD of 120.078 Å compared with the reference. The binding free energy was -9.46 kcal/mol, showing strong favorable interactions, including van der Waals forces, hydrogen bonds, desolvation, and electrostatics. Notably, the intermolecular energy from vdW and hydrogen bonds was -11.14 kcal/mol, highlighting the robust DMC-DHFR interaction. Despite a positive torsional energy contribution (+1.79 kcal/mol), the stable binding suggests that DMC effectively engages DHFR, adapting to its active-site dynamics while remaining stable. The estimated inhibition constant (Ki) was 116.59 nM, indicating ligand potency (Figures 2–5).

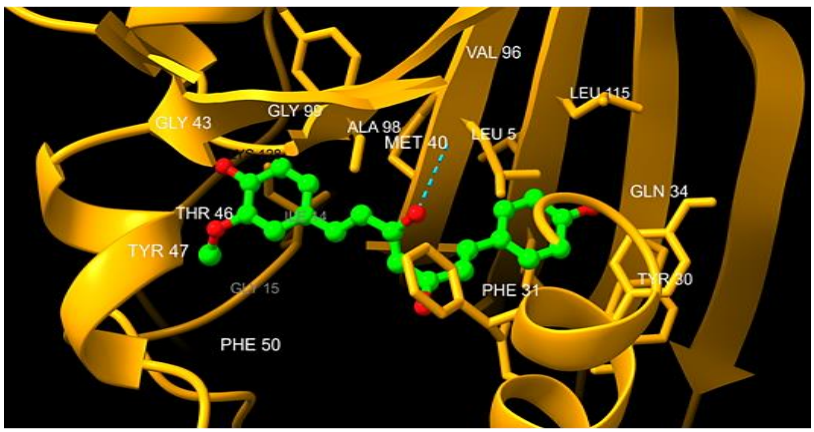

Figure 2. Represents the interaction of DMC with DHFR visualized in ChimeraX.

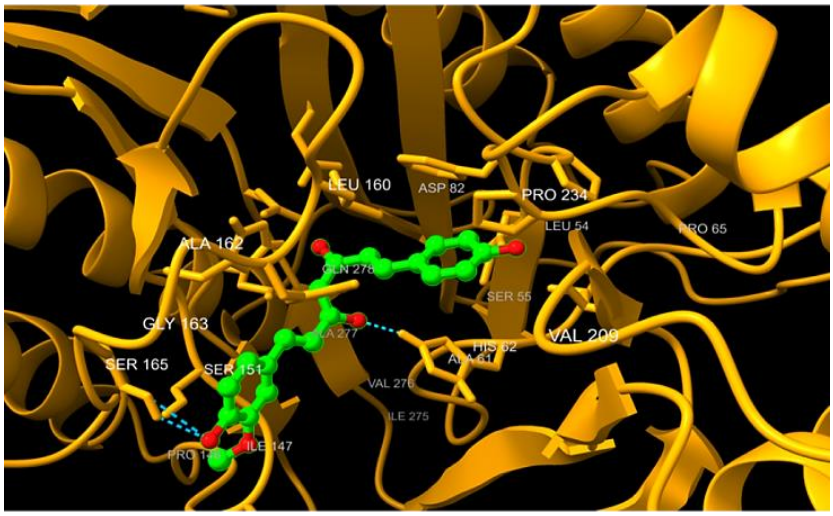

Figure 3. Represents the interaction between DMC and methionine aminopeptidase visualized in ChimeraX.

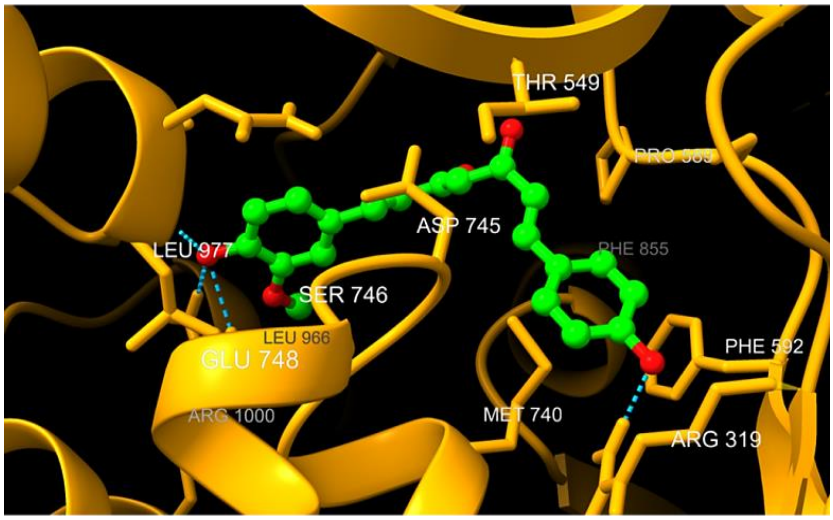

Figure 4. Represents the interaction between DMC and COX-2 visualized in ChimeraX.

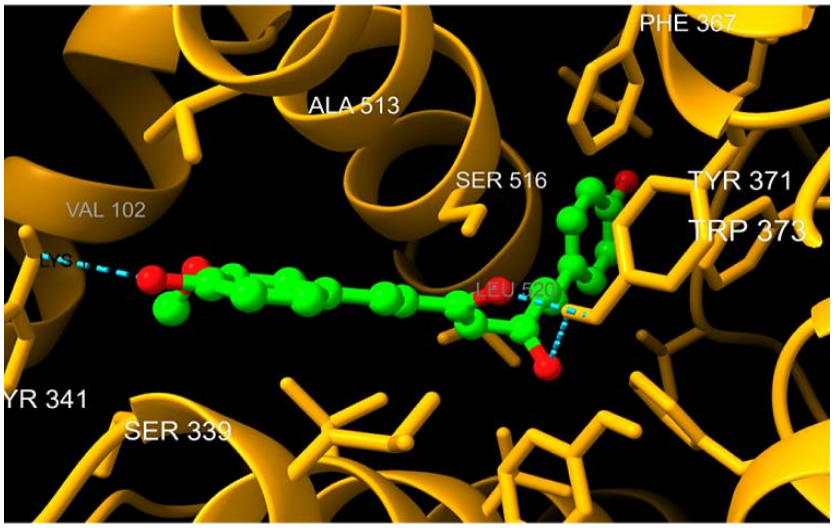

Figure 5. Represents the interaction between DMC and SARS-CoV-2 Omicron visualized in ChimeraX.

Alzheimer's Disease—Methionine Aminopeptidase from *Pyrococcus furiosus* (PDB ID: 6LVH)

Docking demethoxycurcumin with the Alzheimer's disease target protein resulted in a docked complex with a reasonable structural alignment (RMSD 77.792 Å) to the reference. The calculated binding free energy was -8.06 kcal/mol, with favorable interactions (vdW and hydrogen bonds). The intermolecular energy, including vdW and hydrogen bonds, was -10.03 kcal/mol, indicating favorable binding interactions with Methionine Aminopeptidase. The stable binding conformation (total internal energy -0.84 kcal/mol) and low inhibition constant (Ki 1.24 uM) underscore demethoxycurcumin's strong potential as an Alzheimer's disease inhibitor**.**

Anti-inflammatory Inhibition of Cyclooxygenase-2 (COX-2)

Molecular docking of DMC with COX-2, a key inflammatory enzyme, demonstrated a reasonable structural alignment (RMSD 68.966 Å) to the reference. The calculated binding free energy was -10.35 kcal/mol, signifying robust interactions (vdW, hydrogen bonds, and electrostatic). This value considers intermolecular energy contributions, including vdW, hydrogen bonds, desolvation, and electrostatics. The intermolecular energy, combining vdW and hydrogen bond interactions, was -12.10 kcal/mol, underscoring favorable binding between DMC and COX-2. The stable binding conformation (total internal energy -0.75 kcal/mol) and low inhibition constant (Ki 26.08 nM) suggest it as a potent anti-inflammatory drug development.

SARS-CoV-2 Omicron BA.1 (PDB ID: 8H3M)

Molecular docking of DMC with the COVID-19 SARS-CoV-2 Omicron variant. This yielded a Cluster Rank 1 conformation with an RMSD of 334.741 Å, indicating a reasonable alignment. The binding free energy was -9.30 kcal/mol, indicating a stable conformation. The intermolecular energy (vdW, hydrogen bonds, desolvation) was -11.09 kcal/mol, with additional favorable electrostatic energy (-0.37 kcal/mol). The docked complex's total internal energy was -0.84 kcal/mol, signifying stable binding. Despite the positive torsional energy (+1.79 kcal/mol), the overall binding energy remained favorable. The DMC-SARS-CoV-2 Omicron variant interaction had a Ki of 151.88 nM at 298.15 K, highlighting its high potency.

ADME Properties of DMC

ADME prediction for demethoxycurcumin (DMC) using the SwissADME web tool provides insights that align with the Lipinski Rule of Five, indicating its potential as a promising drug candidate. Notably, DMC's strong likelihood of DMC gastrointestinal absorption complements its overall drug-like profile, making it a compelling candidate for drug development (Table 2).

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Table 2. Predicted physicochemical and ADME properties of DMC.

Compound	Log S (ESOL)	Log P	TPSA (Å2)	HBD	Molar mass	GI absorption
DMC	-3.90	2.85	86.99	3	340	High

**ESOL= estimated solubility, Log P= lipophilicity, TPSA= topological polar surface area, HBD= hydrogen bond donor, GI= gastrointestinal*

CONCLUSION

In conclusion, we employed molecular docking simulations to explore demethoxycurcumin (DMC) interactions with diverse target proteins, including Dihydrofolate Reductase (DHFR), Methionine Aminopeptidase, Cyclooxygenase-2 (COX-2), and the SARS-CoV-2 Omicron variant. The results indicate promising binding affinities and interactions, implying DMC's potential of DMC as a versatile therapeutic agent.

DMC displayed robust binding with DHFR, suggesting its potential as an anticancer agent by inhibiting this vital cancer therapy target. Its interaction with Methionine Aminopeptidase indicated possible neuroprotective effects for Alzheimer's treatment through protein processing modulation. Effective interaction with COX-2's active site highlighted DMC's anti-inflammatory potential of DMC. Interaction with SARS-CoV-2 Omicron variant proteins suggested antiviral potential, warranting further validation.

Additionally, ADME predictions aligned with DMC's suitability as a drug candidate, adhering to Lipinski's criteria and exhibiting favorable characteristics.

Collectively, our findings suggest that DMC is a promising treatment for cancer, neurodegenerative diseases, inflammation, and potential viral infections. These results form a basis for further experimental and preclinical investigations exploring DMC's potential of DMC as a versatile therapeutic agent in various medical contexts**.**

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