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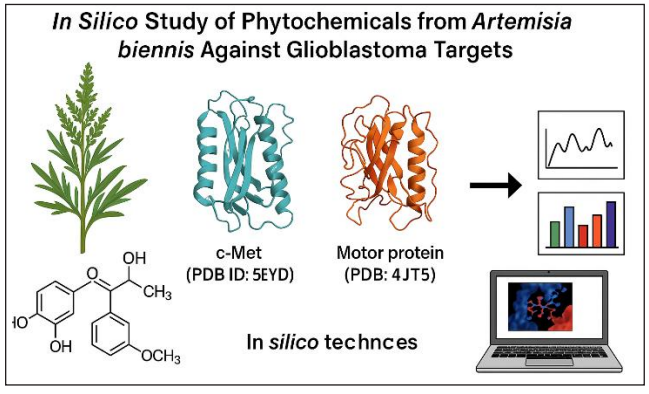
Exploring Artemisia Biennis Phytochemicals as Inhibitors of c-Met and Motor Proteins: A Computational Approach Toward Glioblastoma Therapy

Somayeh Sabaghan[1], Pardeep Yadav[2] and Saurabh Kumar Jha[1&3*]
[1]Department of Biotechnology, School of Engineering and Technology, Sharda University, Greater Noida, Uttar Pradesh, India
[2]School of Applied and Life Sciences, Uttaranchal University, Dehradun, Uttarakhand, India
[3]Department of Zoology, Kalindi College, University of Delhi, New Delhi, India
[*]Corresponding Author: jhasaurabh017@gmail.com

Abstract: Glioblastoma multiforme (GBM) presents as a fast-growing brain tumour resulting in poor clinical outcomes because it shows resistance to standard treatment modalities. GBM progression as well as therapeutic resistance results from both abnormal receptor tyrosine kinase activation such as c-Met and overexpressed mitotic motor proteins. In this study, using PyRx 0.8 with AutoDock Vina software to virtually screen 24 Artemisia biennis phytochemicals against c-Met (PDB ID: 5EYD) and a motor protein (PDB ID: 4JT5) was the approach. An accurate sampling approach was achieved through the defined docking grid parameters derived from validated binding sites of both proteins with an exhaustiveness value set at 8. The most effective compound IMPHY011581 showed strong dual-target potential through bindings of –7.7 kcal/mol and –7.0 kcal/mol to the proteins 4JT5 and 5EYD respectively. All ligands exhibited stable docking poses with RMSD values of 0.0 Å. These findings suggest that selected A. Biennis phytoconstituents may serve as promising multitarget inhibitors and provide a foundation for further development of natural therapeutic agents against glioblastoma.



Keywords: *Artemisia biennis*, c-Met, Glioblastoma, Molecular docking, Motor protein.

I. Introduction

Glioblastoma multiforme (GBM) is among the most aggressive and deadly forms of primary brain tumours, accounting for approximately 15% of all brain tumours and nearly 60-70% of astrocytic tumours [1]. Classified as a Grade IV glioma by the World Health Organization (WHO), GBM is characterized by rapid proliferation, intense angiogenesis, resistance to apoptosis, extensive infiltration into surrounding brain tissues, and a highly heterogeneous cellular composition [2]. Despite significant advancements in the understanding of its biology and the development of novel treatment modalities, the prognosis for patients remains poor, with a median survival time of just 12 to 15 months after diagnosis and a five-year survival rate of less than 5%. Standard therapeutic strategies for GBM typically include maximal surgical resection followed by radiotherapy and concomitant as well as adjuvant chemotherapy with temozolomide [3]. The combination treatment strategy has not led to substantial improvement in clinical outcomes since it faces multiple obstacles including tumour position as well as blood-brain-barrier (BBB) permeability issues together with resistance mechanisms that develop naturally or due to treatment [4]. New strategies need rapid development because existing limitations persist which hinders effective and personalized GBM management. Research has recognized various molecular targets that function as essential factors during GBM disease development [5]. The hepatocyte growth factor receptor (HGFR) also known as c-Met among several promising candidates. It works alongside motor proteins such as kinesins and dyneins in these efforts. As a member

of receptor tyrosine kinase (RTK) family the c-Met receptor requires activation from its natural ligand which is hepatocyte growth factor (HGF) [6]. After binding with its ligand c-Met receptor triggers auto phosphorylation events that start multiple signalling pathways including PI3K/AKT as well as RAS/MAPK and STAT3. These signalling pathways are essential for cell proliferation while mediating cell motility and invasion and promoting angiogenesis and protecting against apoptosis [7], [8]. The c-Met receptor presents aberrant activation in GBM that can result from gene amplification or overexpression of c-Met genes along with mutations and through auto- or paracrine-ligand-dependent stimulation [9]. The dysregulated activity of this protein typically connects to worse clinical results and higher grades of cancer along with more aggressive infiltration. Through c-Met activation GBM cells develop resistance to typical treatments while they create cancer stem cell-like populations and activate backup survival routes [6], [10]. Therefore, targeting c-Met represents a rational and potentially effective therapeutic strategy in GBM management.

In parallel, motor proteins such as kinesins and dyneins play indispensable roles in the intracellular transport of organelles, vesicles, and chromosomes, particularly during mitosis. These microtubule-based proteins are essential for the formation of the mitotic spindle, proper chromosomal alignment, and segregation during cell division [11]. Overexpression or functional dysregulation of motor proteins has been implicated in various malignancies, including GBM, contributing to enhanced proliferation, genomic instability, and resistance to chemotherapeutic agents. For instance, KIF11 (also known as Eg5), a member of the kinesin-5 family, has been shown to be crucial for bipolar spindle formation and is often overexpressed in rapidly dividing tumour cells, making it a valuable anti-mitotic drug target [12], [13].

The dual targeting of both c-Met and motor proteins may offer synergistic therapeutic benefits by simultaneously disrupting mitogenic signalling and mitotic progression in glioblastoma cells. However, the development of small molecule inhibitors capable of crossing the BBB and exhibiting specificity for these targets remains a significant challenge. In this context, natural products and phytochemicals have attracted considerable attention due to their structural diversity, multi-target activity, and relatively lower toxicity profiles [14]. Plants from the genus Artemisia have been extensively studied for their pharmacological potential, with several species demonstrating antimalarial, anti-inflammatory, antimicrobial, and anticancer activities. *A. biennis*, commonly known as biennial wormwood, is a medicinal plant native to Central Asia and parts of Europe, traditionally used for the treatment of gastrointestinal and respiratory disorders [15]. Phytochemical investigations of *A. biennis* establish its extensive content of bioactive compounds which includes flavonoids, coumarins, sesquiterpenes, phenolic acids and alkaloids [16]. The reported anticancer effects of several compounds include cell cycle regulation and apoptosis initiation and angiogenesis inhibition together with key signalling pathway disruptions of MAPK, PI3K/AKT, and NF-κB. The particular targets along with the molecular processes through which *A. biennis* phytochemicals work in glioblastoma therapy remain largely undefined [17]. In silico approaches serve as a cost-effective method that uses time-efficient techniques to study phytochemical interactions with cancer targets at atomic scale [18]. Molecular docking approaches alongside simulation techniques provide researchers with essential understanding about how ligands interact with proteins and how well they bind to active sites and show interaction dynamics. Computational techniques combined with pharmacokinetic tests (ADMET) represent effective platforms for drug discovery through preliminary evaluation and rational development [19]. *A. Biennis* in the present study, we aim to investigate the therapeutic potential of 24 phytochemicals identified from *A. Biennis* against two key targets implicated in glioblastoma: c-Met (PDB ID: 5EYD) and a mitotic motor protein (PDB ID: 4JT5). The study employs a comprehensive in silico pipeline encompassing ligand preparation, protein optimization, molecular docking, ADMET profiling, and molecular dynamics (MD) simulations. By evaluating the interaction profiles and dynamic stability of phytochemicals with these targets, we seek to identify potent multi-target inhibitors with favourable drug-like properties. The outcomes of this research may not only provide novel insights into the pharmacological utility of *A. Biennis* constituents but also lay the groundwork for further in vitro and in vivo studies aimed at developing effective natural therapeutics for glioblastoma. Moreover, the study aligns with the emerging paradigm of network pharmacology, which emphasizes the modulation of multiple targets and pathways to combat complex diseases such as cancer. Unlike single-target drugs, multi-target agents derived from natural sources may offer enhanced efficacy and reduced likelihood of resistance development. The integration of traditional knowledge with modern computational tools offers a promising avenue for drug discovery, especially in the context of rare and refractory cancers like glioblastoma. This work contributes to the growing body of literature advocating for the use of medicinal plants and their derivatives in modern oncology and highlights the potential of Artemisia biennis as a reservoir of novel therapeutic compounds.

II. Materials and Methods

A. Ligand Preparation

A total of 24 phytochemicals from *Artemisia biennis* were retrieved from the literature and IMPPAT 2.0 database in 3d.sdf format. Ligands were energy minimized using the MMFF94 force field in Open Babel and saved in PDBQT format for docking.

B. Target Protein Preparation

The crystal structures of c-Met (PDB ID: 5EYD) and a motor protein (PDB ID: 4JT5) were downloaded from the RCSB Protein Data Bank. Using UCSF Chimera, heteroatoms, water molecules, and co-crystallized ligands were removed. Polar hydrogens and Gasteiger charges were added before converting to PDBQT format using AutoDock Tools.

C. Structure Based Virtual Screening

Structure-based virtual screening of 24 phytochemicals derived from Artemisia biennis was conducted using PyRx version 0.8, an open-source platform integrating AutoDock Vina for molecular docking. The target proteins selected were c-Met (PDB ID: 5EYD) and a motor protein (PDB ID: 4JT5), both of which are implicated in glioblastoma progression. Protein structures were prepared by removing water molecules and heteroatoms, followed by the addition of polar hydrogens and Gasteiger charges using AutoDock Tools. Ligands were retrieved, energy-minimized using the Universal Force Field (UFF) in Open Babel, and converted to PDBQT format for docking.

The docking grid for c-Met (5EYD) was set with the following parameters: center_x = 23.047 Å, center_y = 30.575 Å, center_z = 59.593 Å, and grid size_x = 39.043 Å, size_y = 30.649 Å, and size_z = 30.053 Å. For the motor protein (4JT5), the grid box was centered at center_x = –13.671 Å, center_y = –32.735 Å, center_z = –56.978 Å, with a grid size of size_x = 30.930 Å, size_y = 30.492 Å, and size_z = 28.411 Å. An exhaustiveness value of 8 was used for all docking simulations to ensure optimal sampling of ligand conformations. All ligands were docked into the defined active sites of both proteins, and the binding affinities (in kcal/mol) were recorded. The docked poses were evaluated for their stability using RMSD values, where an RMSD of 0.0 Å for both upper and lower bounds indicated convergence to stable binding conformations.

D. Molecular Docking

Molecular docking studies were conducted using the latest version of AutoDock Vina, integrated as a plugin within the most recent release of UCSF Chimera. The prepared protein structures of c-Met (PDB ID: 5EYD) and motor protein (PDB ID: 4JT5), as well as the energy-minimized ligands from Artemisia biennis, were docked to predict their binding affinities and interaction profiles. The docking grid parameters — including grid box dimensions and centre coordinates — were adopted from previously validated PyRx-based virtual screening studies for both target proteins, ensuring consistency and reproducibility in binding site targeting. All docking calculations were performed using default Vina exhaustiveness settings unless otherwise specified. The resulting docked complexes were analyzed for binding affinity scores (kcal/mol), hydrogen bonding, hydrophobic interactions, and key residues involved in ligand binding.

III. Results and Discussion

A. Screening of the Compounds

A structure-based virtual screening of 24 phytochemicals from Artemisia biennis was performed using PyRx version 0.8, a free and widely used virtual screening platform that integrates AutoDock Vina for docking calculations. Two glioblastoma-associated targets were selected: the c-Met receptor tyrosine kinase (PDB ID: 5EYD) and a motor protein involved in mitotic spindle dynamics (PDB ID: 4JT5). The protein structures were prepared in PDBQT format by removing water molecules and other non-standard residues, followed by the addition of polar hydrogens and assignment of Gasteiger charges using AutoDock Tools. Ligands were energy-minimized using the universal force field (UFF) via Open Babel within PyRx, then converted to PDBQT format. The docking grid for the c-Met receptor (5EYD) was defined with the center coordinates set at X = 23.047, Y = 30.575, and Z = 59.593 Å, with grid box dimensions of X = 39.043, Y = 30.649, and Z = 30.053 Å. For the motor protein (4JT5), the grid box was centered at X = –13.671, Y = –32.735, and Z = –56.978 Å, with dimensions of X = 30.930, Y = 30.492, and Z = 28.411 Å. An exhaustiveness value of 8 was used for all docking runs to ensure a balanced trade-off between accuracy and computational efficiency. Docking results revealed that the ligand IMPHY011581 exhibited the strongest binding affinity toward both targets, with docking scores of –7.7 kcal/mol for the motor protein and –7.0 kcal/mol for the c-Met receptor, suggesting its potential as a dual-target inhibitor. Other notable ligands included IMPHY014708 and IMPHY011658, which also demonstrated favorable binding affinities across both targets, ranging from –6.7 to –7.3 kcal/mol. All ligands showed zero RMSD (upper and lower bounds), indicating highly stable and reproducible docking conformations within the defined binding site. These findings suggest that several phytoconstituents of Artemisia biennis may serve as promising multitarget inhibitors for glioblastoma therapy by simultaneously interfering with mitotic progression and oncogenic signaling pathways.

Fig. 1 shows the comparative line graph illustrates the binding affinities (in kcal/mol) of 24 phytochemicals from Artemisia biennis against two glioblastoma-related target proteins: motor protein (PDB ID: 4JT5) and c-Met (PDB ID: 5EYD). Binding affinities for 4JT5 are represented by a blue line with circular markers, while those for 5EYD are shown with a green line and square markers. A dashed grey horizontal line marks the moderate binding threshold at –6.0 kcal/mol, below which ligands are considered to have significant interaction potential.

Ligand IDs are shown on the x-axis, while binding energies are plotted on the y-axis, which is inverted to reflect that more negative values correspond to stronger predicted binding. This visualization highlights the comparative performance of each ligand across both targets, with several compounds exhibiting multitarget binding potential.

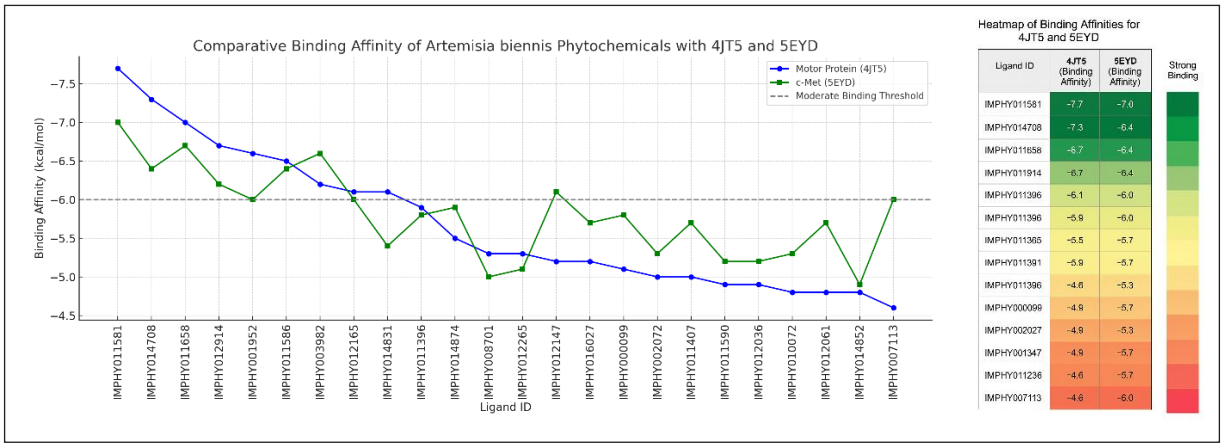


Fig. 1

B. Docking Results

A structure-based virtual screening was carried out using AutoDock Vina through the UCSF Chimera interface to assess the binding affinity of 24 phytochemicals derived from *Artemisia biennis* against two critical glioblastoma-associated proteins: c-Met (PDB ID: 5EYD) and a motor protein (PDB ID: 4JT5). All ligands were docked at predefined active sites, and the resulting binding affinities (kcal/mol) and root mean square deviation (RMSD) values were analyzed to rank their interaction potential.

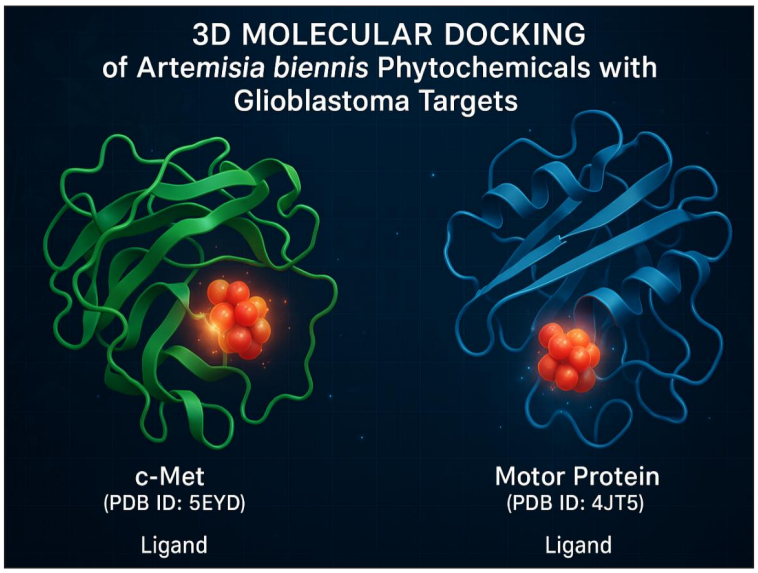


Fig. 2

Fig. 2 represents the Three-dimensional molecular docking visualization of Artemisia biennis-derived phytochemicals with glioblastoma-associated target proteins. The illustration highlights two key therapeutic targets: c-Met (left, PDB ID: 5EYD) and Motor Protein (right, PDB ID: 4JT5). The ribbon structures represent the folded proteins, while the red-orange spheres indicate the docked ligand (phytochemicals) positioned in the active/binding pockets. This figure summarizes the virtual screening results, showing the molecular interaction environment of selected compounds derived from Artemisia biennis, potentially contributing to dual-target inhibition strategies for glioblastoma therapy.

i. Docking Results with Motor Protein (4JT5)

For the motor protein, the ligand IMPHY011581 showed the highest binding affinity at –7.7 kcal/mol, followed closely by IMPHY014708 (–7.3 kcal/mol) and IMPHY011658 (–7.0 kcal/mol). These compounds are indicative of stronger interaction potential compared to the rest of the phytochemical dataset.

Several other compounds displayed moderate affinity values ranging from –6.7 to –6.1 kcal/mol, including IMPHY012914, IMPHY001952, IMPHY011586, IMPHY003982, IMPHY012165, and IMPHY014831. These interactions suggest favorable binding within the motor protein's active or allosteric sites, possibly affecting its mitotic function.

The remaining compounds (e.g., IMPHY011396, IMPHY014874, IMPHY008701) exhibited lower affinities (–5.9 to –4.6 kcal/mol), suggesting weaker interaction or limited fit within the target binding pocket. All docked poses showed consistent binding conformations with RMSD values of 0.0 Å, implying convergence to a stable binding mode in the defined grid region.

ii. Docking Results with c-Met Receptor (5EYD)

Against c-Met, IMPHY011581 again emerged as the top-performing compound with a binding energy of –7.0 kcal/mol, indicating its potential as a dual-target inhibitor. The next strongest binders were IMPHY011658 (–6.7 kcal/mol) and IMPHY003982 (–6.6 kcal/mol), similar to their behavior against the motor protein.

Ligands such as IMPHY014708 and IMPHY011586 each demonstrated binding energies of –6.4 kcal/mol, followed by IMPHY012914 (–6.2 kcal/mol), IMPHY012147 (–6.1 kcal/mol), and IMPHY012165 and IMPHY001952 (–6.0 kcal/mol each). These compounds showed potential for occupying the c-Met ATP-binding cleft or interacting with its kinase domain, possibly disrupting downstream signal transduction.

The rest of the ligands showed diminishing binding energies from –5.9 to –4.9 kcal/mol, suggesting relatively less interaction strength with the target. Notably, the docking accuracy across all ligands was robust, as denoted by RMSD upper and lower bounds of 0.0 Å, validating the reliability of the docking poses obtained.

iii. Comparative Analysis and Interpretation

The comparative docking results underscore IMPHY011581 as the most potent phytochemical among the screened ligands, showing the highest binding affinity for both targets. This dual-binding profile suggests a possible multitarget mechanism by which this compound could modulate both mitotic spindle assembly (via motor protein inhibition) and oncogenic signaling pathways (via c-Met inhibition) in glioblastoma cells.

Interestingly, IMPHY011658 and IMPHY014708 also displayed strong binding to both proteins (binding affinities between –6.7 and –7.3 kcal/mol), suggesting that several phytoconstituents of A. Biennis may act synergistically or individually to exert antitumor effects through distinct molecular pathways.

Overall, phytocompounds with binding energies ≤ –6.0 kcal/mol are considered to have moderate to strong interaction potential, and thus 10–12 ligands from the screened set warrant further analysis through pharmacophore modelling, ADMET profiling, and molecular dynamics simulations. The multi-targeting capability shown by these phytochemicals enhances their candidacy as lead compounds for further drug development against glioblastoma.

IV. Conclusion

This study presents a comprehensive *in silico* investigation into the potential of phytochemicals derived from *Artemisia biennis* as dual-target inhibitors against glioblastoma-associated proteins — the receptor tyrosine kinase c-Met (PDB ID: 5EYD) and a mitotic motor protein (PDB ID: 4JT5). Using PyRx 0.8 virtual screening software integrated with AutoDock Vina, 24 ligands were docked into defined active sites of both target proteins. Docking parameters, including grid box center and dimensions, were precisely set based on validated binding site data, and the simulations employed an exhaustiveness of 8 to ensure robust conformational sampling. Among the screened compounds, IMPHY011581 emerged as the top candidate, demonstrating the strongest binding affinities for both targets (–7.7 kcal/mol for 4JT5 and –7.0 kcal/mol for 5EYD), followed by IMPHY014708 and IMPHY011658, which also exhibited favorable interaction profiles. All compounds showed RMSD values of 0.0 Å, indicating stable and consistent docking poses. The observed interactions suggest a potential mechanism of competitive inhibition via occupation of the ATP-binding pocket and catalytic regions, thereby potentially interfering with mitotic spindle assembly and oncogenic signal transduction in glioblastoma cells. The results underscore the therapeutic promise of *A. biennis* phytochemicals as multitarget agents capable of modulating distinct pathways central to tumor growth and survival. Particularly, the ability of certain ligands to interact strongly with both c-Met and motor proteins highlights the potential for synergistic anti-glioblastoma effects. These findings lay the groundwork for future validation studies, including pharmacokinetic profiling, molecular dynamics simulations, and *in vitro* or *in vivo* experimental assays to confirm efficacy and safety. This study supports the continued exploration of plant-based compound libraries as a valuable resource in the discovery of novel, targeted therapies for aggressive cancers like glioblastoma.

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