



## Molecular docking study of Cytochalasin H and Fascin interactions as prospective targets for gastric cancer

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### Abstract

**Background:** Gastric cancer is the fifth most common neoplasm and the fourth leading cause of mortality worldwide. Incidence rates vary widely and depend on risk factors, epidemiological factors, and carcinogenesis patterns. Understanding the molecular mechanisms underlying cancer progression and metastasis is crucial for developing effective therapeutic strategies. Previous studies have reported that fascin overexpression, an actin-binding protein, promotes cell motility and invasion in cancers by bundling actin filaments. Therefore, inhibiting this protein can be a major step in treatment.

**Methods:** In this prospective study, the protein structure of fascin was obtained from the Protein Data Bank (PDB). Using the HyperChem 7.0 software, the chemical structure of cytochalasin H as a small molecule inhibitor was designed. Rigid docking studies between cytochalasin H and fascin protein were performed using the AutoDock Vina 1.1.2 software, and the obtained results were analyzed using LigPlot+ v.1.4.5, Discovery Studio 4.5, and PyMOL v.1.9 software.

**Results:** According to the analyses and the obtained results, cytochalasin H and fascin protein have an effective interaction with an optimal energy level.

**Conclusion:** These findings suggest that cytochalasin H may be developed into a potential chemotherapeutic drug for the treatment of gastric cancer by inhibiting fascin. Nevertheless, further in vitro and in vivo experiments are necessary to elucidate the exact mechanism.

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### Highlights

#### What is current knowledge?

Fascin, an actin-binding protein, promotes cell motility and invasion in breast, colorectal, and gastric cancers by bundling actin filaments together.

#### What is new here?

Few studies have been conducted on the inhibitory effect of cytochalasin H and its interactions with cytoskeleton proteins. Therefore, this article addresses the possibility that inhibiting fascin by cytochalasin H could substantially impact treatment approaches for gastric cancer.

### Introduction

Gastric cancer is a prevalent and aggressive form of cancer that accounts for 8.3% of cancer-related deaths and affects individuals worldwide, with a particularly high incidence among males (1,2). According to the International Classification of Diseases for Oncology (ICD-O), gastric cancer is identified by the specific code 8602/0, characterizing the disease based on its histological and morphological features (3). Gastric carcinoma is a complex disease influenced by various factors, including both environmental and genetic risk factors (4). One of the significant challenges in treating gastric cancer is its tendency to metastasize, which hinders successful treatment outcomes (5). Cell motility and adhesiveness play crucial roles in the aggressive nature of gastric cancer, as they cause the rearrangement of the cytoskeleton structure (6). The cytoskeleton, comprised of the microtubule and microfilament systems, mainly relies on actin-bundling proteins, such as cortactin and fascin (7). These proteins are instrumental in regulating the organization and stability of the cytoskeleton. Fascin comprises two chains and four B-trefoil domains with a length of 496 sequences. Recent studies have provided evidence that fascin protein acts as a metastasis promoter and plays a crucial role in regulating cell migration through cellular signaling pathways (8,9). Overexpression of this protein has been documented in various types of tumors, including breast, bladder, prostate, brain tumors, and esophageal carcinoma (10). In these cancers, fascin overexpression is associated with enhanced cell invasion and metastasis of tumor cells to surrounding tissues and has been identified as a prognostic marker in gastric cancer (11,12). In a detailed crystal structure of fascin, ligand molecules, such as glycerol and polyethylene glycol, are found to be bound within pockets in the two primary actin-binding sites. These molecules offer insights for the strategic development of novel anticancer fascin inhibitors.

In contrast, cytochalasin compounds affect the cytoskeleton by targeting microfilaments and microtubules, disrupting actin polymerization processes

(13,14). Cytochalasins belong to a class of alkaloid mycotoxins and are commonly found in fungi, with extraction often performed from an endophytic fungus called *Rhizoglyphus* sp. (15). Unlike conventional chemotherapy drugs, which often lead to severe side effects, drug resistance, and suboptimal long-term outcomes, secondary metabolites like cytochalasin H exhibit high biological activity and low toxicity. Cytochalasin H, as a metabolite of *Phomopsis paspali*, has shown significant effects on cytoskeleton reorganization and its anti-inflammatory, antifungal, and antitumor properties have been reported (16). In addition, its antitumor effects are achieved through distinct mechanisms, including the induction of apoptosis and the inhibition of angiogenesis (17,18,19). In the present study, we employed in silico analyses to explore potential interactions between cytochalasin H (inhibitor) and fascin. Blocking fascin binding sites is considered a vital target for antimetastatic drugs. Our study shows that cytochalasin H has the potential to inhibit cell migration as a secondary metabolite by blocking this protein. Molecular docking is a widely used method in drug discovery and cancer research to investigate the stable interaction between small molecules and proteins (20). This approach holds a valuable preclinical tool for the development of more effective and potent anticancer therapies (21).

### Methods

The two-dimensional structure of cytochalasin H as a ligand was designed and optimized using the HyperChem 7.0 software (22) and the Polak-Ribiere algorithm to achieve the most stable structure. The ligand molecule in HIN format was converted to the Protein Data Bank (PDB) format using Open Babel 2.4.1 tool (22). This format is compatible with the PDB. The crystal structure of the human target protein fascin with a resolution of 2Å was obtained from the Brookhaven PDB (Code: 3p53). Discovery Studio software was used to remove water molecules and default ligands from the fascin protein structure. This step prepares the protein for further analysis. AutoDock Tools 1.5.6, part of the molecular graphics laboratory (MGL) software package, was used to convert the pre-processed fascin protein structure from PDB to PDB, Partial Charge (Q), and Atom Type (T) (PDBQT) format. PDBQT is the format required for AutoDock Vina, the docking software used in the study (23).

We performed rigid docking to predict atomic-level interaction between cytochalasin H and fascin protein by AutoDock Vina 1.1.2. (<http://vina.scripps.edu>). The results obtained from docking were analyzed using various software tools, such as LigPlot+ v.1.4.5, Discovery Studio 4.5, and PyMOL v.1.9. These tools provide visualization and analysis of the ligand-protein interactions, allowing for a more detailed understanding of the binding mode and potential binding sites.

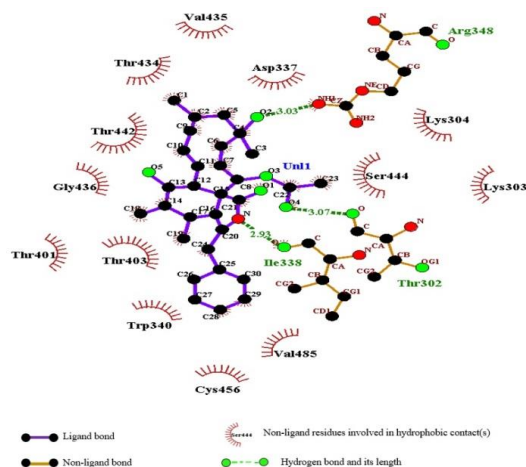
## Results

Cytochalasins have been found to impact various cellular functions, drug delivery, and chemotherapy. They can also induce a significant clinical response in cell systems as antitumor drugs (8). The molecular binding position between the ligand and protein was determined in the present study using a grid box. This function plays a crucial role in the selection and efficiency of molecular docking by restricting the search area in AutoDock. The coordinates of the grid box for the ligand binding region (actin-binding site) were set as 27.083 for X, -52.227 for Y, and 33.496 for Z. The size of the grid box was maintained at 42 \* 34 \* 40, with a grid spacing of 0.375 Å. The results obtained from AutoDock Vina 1.1.2 indicated that the affinity value for the interactions between fascin protein and cytochalasin H was determined to be -9.5 kcal/mol (Figure 1).

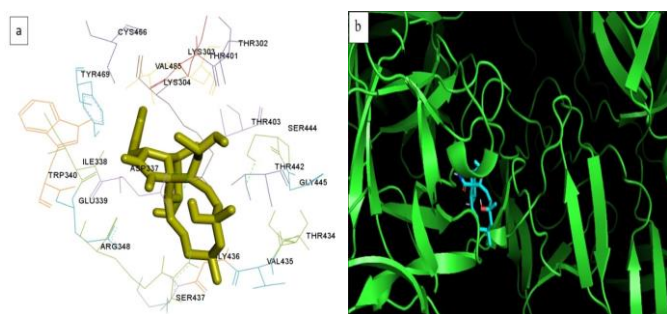
mode	affinity (kcal/mol)	dist from best mode rmsd l.b.   rmsd u.b.
1	-9.5	0.000   0.000
2	-9.3	3.091   4.988
3	-9.1	3.151   5.268

**Figure 1.** Affinity values for cytochalasin H and fascin protein interactions

Cytochalasin H was docked to residues located in the active site of fascin protein. Analysis conducted using LigPlot+ v.1.4.5 software revealed the two-dimensional protein-ligand interactions, as shown in Figure 2. Amino acids present in the active site formed interactions with the ligand. The hydrophobic contacts involved Asp337, Val435, Thr434, Thr442, Gly436, Thr401, Thr403, Trp340, Cys456, Val485, Lys303, Ser444, and Lys304, which played a role in binding cytochalasin H to the fascin protein. Furthermore, three hydrogen bonds were observed with Arg348, Thr302, and Ile338. Among them, the hydrogen bond with Ile338 had a length of 2.93 Å and was related to a hydrophobic residue. Two hydrogen bonds, with lengths of 3.03 Å and 3.07 Å, were formed with the polar aliphatic residues Arg348 and Thr302, respectively, as depicted in Figure 2. The primary bonds responsible for stabilizing the ligand-enzyme complex were hydrogen bonds and hydrophobic interactions (24).



**Figure 2.** Examining the amino acids involved in the formation of hydrogen bonds (green dashed line) and hydrophobicity ( ) in the reaction of fascin protein with cytochalasin H by LigPlot software.



**Figure 3.** A) the three-dimensional interaction between an inhibitory molecule (yellow color) and the protein active site by Discovery Studio software. B) The three-dimensional interaction between an inhibitory molecule (blue color) in the protein active site by PyMOL software.

In this study, Discovery Studio 4.5 and PyMOL v.1.9 software was used for the three-dimensional analysis of molecular docking results. Figure 3a shows the ligand and protein interaction in the active site. Cytochalasin H is at its best energy level with the fascin protein. High-quality images were obtained from the ligand binding site to the protein. Figures 3a and 3b show an active site in the protein. This site is located at the interface between chain A and chain B.

Therefore, based on these results, cytochalasin H can be introduced as an effective antitumor agent in gastric cancer. However, further studies are needed to explore the exact mechanism.

## Discussion

Given that gastric cancer is a multifactorial disease associated with high mortality rates, numerous studies have employed molecular docking to predict suitable drugs. In a study by Imani-Saber et al. in 2015, imatinib was proposed as a suitable ligand to inhibit casein kinase 2 (CK2) and preserve promyelocytic leukemia (PML) as a tumor suppressor gene, focusing on gastric cancers caused by *Helicobacter pylori* (24). Also, much attention has been paid to fascin as a crucial actin-bundling protein (F-actin) pivotal in creating cell surface protrusions that facilitate cell migration (20,11). In normal adult epithelial tissues, fascin is typically absent or down-regulated. However, it is notably up-regulated in various carcinomas, demonstrating a positive correlation with invasion, metastasis, and unfavorable prognosis (11,25). Conversely, inhibiting fascin through an inhibitor can prevent the invasion of cancer cells. Multiple studies have investigated the effects of cytochalasins on different types of cancer or infectious diseases (26). The effects of cytochalasin H on apoptosis and migration were investigated in the human lung adenocarcinoma cell line A549. The treatment of A549 cells with cytochalasin H resulted in cell cycle arrest at the G2/M phase and showed strong anti-migratory activities (27). In our study, the main objective was to investigate and understand the underlying interactions through which cytochalasin H inhibits the migration ability of cancer cells, ultimately impeding the progression and metastasis of the disease. In line with this objective, we employed molecular docking techniques to investigate the potential of cytochalasin H as an inhibitor of fascin protein. These findings suggest that cytochalasin H may hold promise as a suitable inhibitor for targeting fascin. This study provides valuable insights into developing therapeutic strategies for gastric cancer treatment by elucidating the molecular interactions and binding energies. However, the precise determination of the inhibitor's concentration, dosage, and efficacy in inhibiting cancer cells requires additional *in vitro* and *in vivo* investigations.

## Conclusion

In conclusion, targeting fascin represents a promising approach for controlling and treating gastric cancer. Inhibition of this protein probably can impact metastasis processes and cytoskeleton polymerization significantly. The docking results demonstrate that cytochalasin H has the potential to serve as a candidate drug for inhibiting and facilitating gastric cancer therapy. So, further investigations, including *in vitro* and *in vivo* studies, are warranted to validate these findings and explore the precise mechanism of action. The development of novel drug design strategies targeting fascin could pave the way for more effective treatments for gastric cancer, another cancer, or even the metastasis of other cancers by influencing the cellular skeleton.

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## Ethical statement

Not applicable. This article was conducted using software and data analysis.

## Conflicts of interest

The authors declared no conflict of interest.

## Author contributions

We confirm that all authors were involved in writing the article. S.H.: A master's graduate, contribution in the manuscript conceptualization, writing, and introduction, and draft preparation; S.A.: A Ph.D. student, contribution in the manuscript methodology, software, writing, and results.

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