



In Silico Evaluation of Microbial Chitinase for Its Anticancer Potential Against Abnormal Glycosylation

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Abstract

Altered glycosylation is a characteristic feature of cancer cells and is closely associated with oncogenesis, malignant transformation, tumor growth and progression, and metastasis. To test the hypothesis that chitinase may interfere with abnormal glycosylation through interactions with UDP-NAG and DPAGT1, the anticancer potential of chitinase from *Thermomyces lanuginosus* was evaluated using molecular docking and protein-protein interaction analyses. The chitinase protein was docked with the ligand UDP-NAG, obtained from the PubChem compound database, and the resulting complexes were evaluated based on docking score, glide score, glide energy, and hydrogen-bond interactions. The obtained docking score and glide energy were -5.568 and -53.491 , respectively, indicating favorable docking of chitinase with the NAG molecule. In addition, protein-protein interaction analysis between chitinase and DPAGT1 revealed favorable structural and scoring models based on balanced, electrostatic-favored, and hydrophobic-favored interactions, suggesting a potentially favorable interaction between the two proteins. The study concludes that chitinase may be a promising candidate for inhibiting carcinogenesis associated with abnormal glycosylation by interacting with UDP-NAG or DPAGT1, which may influence glycosylation pathways.

Keywords:

Chitinase; DPAGT1; UDP-NAG; glycosylation; molecular docking; protein-protein interaction

1. Introduction

Glycosylation is a biological modification process in which carbohydrate moieties are attached to proteins or lipids. The resulting glycoproteins and glycolipids contain abundant carbohydrate moieties in the extracellular region of the cell membrane and play essential roles in cellular processes, including cell adhesion, cell trafficking, and cell signaling [1]. In various studies of carcinogenesis, it was observed that the expression of carbohydrates, or glycans, is distinct in cancer cells compared with normal cells [2,3]. This is attributed to altered expression levels of glycosyltransferases. These enzymes catalyze the formation of

glycosidic linkages by transferring sugar residues to acceptor molecules [4–6]. Abnormal glycosylation drives structural alterations in major glycans, including changes in branching patterns, increased glycan size, and modifications in chemical composition, which can contribute to cancer development [7,8]. Consequently, altered expression of specific glycans, which are often structurally distinct from those in normal cells, is a characteristic feature of cancer cells. Altered glycosylation has been reported to be associated with cancer-related processes, including oncogenesis, malignant differentiation, tumor growth, and metastasis [9–11]. The presence of 1–6 branching between

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N-acetyl-D-glucosamine and mannose residues on N-glycans is among the most extensively studied abnormal glycan structures associated with cancer cell surfaces [12, 13]. N-glycan biosynthesis can be inhibited by targeting DPAGT1, the first committed enzyme in the pathway [14,15]. The transfer of an N-acetyl-D-glucosamine-1-phosphoryl unit from UDP-NAG to dolichyl phosphate (Dol-P) is catalyzed by the dolichyl phosphate N-acetylglucosamine-phosphotransferase (DPAGT1) [10]. The increased branching provides additional sites for glycosylation compared with other N-glycans, resulting in larger, more structurally complex glycans with greater conformational variability [16–18]. The high occurrence of β 1-6 NAG branching is considered a biomarker in many cancers [6,19,20]. DPAGT1 expression and β 1-6 NAG branching have been implicated in oncogenesis and are related to metastasis and poor prognosis, especially in breast cancer, colorectal cancer, and melanoma, as reported in several in vivo studies [21–26]. The therapeutic effects of inhibiting the formation of β 1-6 NAG branching in murine and human tumor cells have been demonstrated through research [23,24]. Despite the importance of N-linked glycans in tumor development and progression from normal cells, immunotherapy targeting N-linked glycans has yet to be established due to the difficulty in accurately distinguishing N-linked glycans between normal and malignant cells [4,27]. The Golgi apparatus facilitates the formation of O- or N-glycan chains through the sequential action of glycosyltransferases [28]. Find-

ing drug-like glycosyl transferase antagonists that inhibit the synthesis of complex branching mechanisms in cancer cells while selectively targeting tumor cells is a difficult task. Chitinase may be further investigated as a potential anticancer candidate for the development of protein therapeutics [29,30]. To investigate its anticancer potential, the hypothesis of chitinase interaction with UDP-NAG and DPAGT1 (dolichyl-phosphate N-acetylglucosamine phosphotransferase 1) at the molecular level was evaluated through in silico analyses, including molecular docking [31] and protein-protein interaction studies.

2. Materials and Methods

2.1. Software

The Schrödinger Maestro interface (Maestro, version 10.5, Schrödinger, LLC, New York, NY, USA, 2019) was used to perform the in-silico docking studies, while the Clus-Pro web server was used for protein-protein interaction analysis [32].

2.2. Retrieval of Sequence for the Three-Dimensional Structure Building

The three-dimensional structure of chitinase from *Thermomyces lanuginosus* was modeled using the primary amino acid sequence (Figure 1) obtained from the National Center for Biotechnology Information (NCBI, www.ncbi.nlm.nih.gov/) under accession number AAY99632.1 [33].

FASTA ▾

chitinase [Thermomyces lanuginosus]

GenBank: AAY99632.1

[GenPept](#) [Identical Proteins](#) [Graphics](#)

```
>AAY99632.1 chitinase [Thermomyces lanuginosus]
MLVKYRVFAPFLWSGLYRRVFCSLHLHTIHAGRVLSPIQEKHAQGYLSVQYFVNWAIYGRNHNPDLP
EKLTHILYAFANVRPDSGEVYLTDTWSDTDKHYPDSWNDTGTNVYGCILQLFLKKRHRKLVLLSIGG
WTYSSNFAQPASTEAGRETFARTATRLVLDLGLDGLDIDWEYPQDDNQARDFVALLRKCREHLDYAAGPN
RRFLLTIACPAGPNFTKLRLPEMTPYLDYFNLMAYNAGSWDQLAGHQANIFPSSTNPASTPFSTDAAL
RHYISVSGVPSSKMVLGMPYGRAFGNTNGPGTPFSGVGEQGWVDYKALPRPGATEHVDPNIGASW
SYDPQTRTMVTYDNVAVAEIKANFVRGAGLGGGMWESSADRGKTANKADGSLIGTFVDGLGGVFALDQ
SPNNLDYPESKYDNLRAFGPGE
```

Figure 1: Amino acid sequence of *Thermomyces lanuginosus* chitinase used to build the three-dimensional structure.

2.3. Three-Dimensional Structure Building Through Homology Modeling and Its Evaluation

The homology modeling technique was used to construct the three-dimensional structure of chitinase from *Thermomyces lanuginosus* using its primary amino acid sequence in FASTA format. The Three-dimensional structure of chitinase from *Aspergillus fumigatus* B1 was used as the template. Homology modeling was performed using the SWISS-MODEL tool (<https://swissmodel.expasy.org/>) [34,35].

2.4. Validation of the Three-Dimensional Modeled Structure Through Ramachandran Plot

The three-dimensional structure of chitinase built through homology modeling was validated using the Ramachandran plot, which evaluates the model based on the phi (ϕ) and psi (Ψ) angles of the amino acid residues [36].

2.5. Preparation of Target/Receptor Protein Molecule for the Docking Study

Protein preparation is the initial step in docking analysis. A Protein Preparation Wizard (version 4.3) was used to prepare the three-dimensional structure generated by homology modeling [37]. The modeled structure of chitinase from *Thermomyces lanuginosus* was prepared by adding hydrogen atoms, removing atomic clashes, removing water molecules, and performing energy minimization [38]. Energy minimization, a crucial step in protein preparation, was performed using the OPLS_2005 force field with an RMSD cutoff of 0.3 Å [39].

2.6. Binding Site Generation in the Target Protein Molecule

The binding site in the target protein molecule was generated using the SiteMap application (version 3.8), which predicts binding sites by analyzing various factors, including site size, tightness, degree of enclosure or exposure, hydrogen-bonding potential, and hydrophobic/hydrophilic characteristics [40].

2.7. Grid Generation and Molecular Docking Studies

2.7.1. Grid Generation in the Target Molecule

Grid generation for the target molecule is an important step in molecular docking, as it determines the size and location of the active or binding site. The grid was generated using the receptor grid generation program with a box size of $20 \times 20 \times 20$ Å. The atoms with a partial atomic charge of less than 0.25 were scaled using van der Waals radii of 1.0 Å [41].

2.7.2. Molecular Docking Studies of the Receptor Molecule with the Ligand

The structure of the ligand UDP-NAG was obtained from the PubChem compound database (Figure 2A). Molecular docking between the target protein and the ligand was performed using Glide (version 7.0). The docking analysis was performed using the standard precision (SP) algorithm [42]. The molecular docking results were expressed as docking scores, which estimate the favorability of ligand and binding at the predicted binding site [43,44].

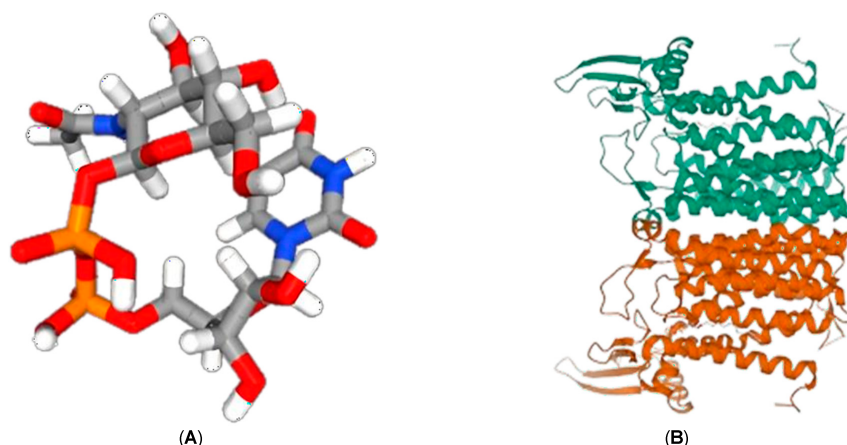


Figure 2: Structure of UDP-NAG (A) and DPAGT1 (B) obtained from PubChem and PDB, respectively.

2.8. Protein-Protein Interaction Between Modeled Chitinase (Ligand) and DPAGT1

The chitinase protein from *Thermomyces lanuginosus* was generated via homology modeling, whereas DPAGT1 was retrieved from the Protein Data Bank under PDB ID 6FM9 (Figure 2B). Protein-protein interaction between the modeled chitinase and DPAGT1 protein was performed using the ClusPro web server. ClusPro (<https://cluspro.org>) is a widely used platform for protein-protein docking studies. The results were analyzed based on the top-ranked model and its corresponding coefficient scores [45].

3. Results and Discussion

3.1. Molecular Docking Studies of Chitinase

The availability of the three-dimensional structure of chitinase from *Thermomyces lanuginosus* was examined in the Protein Data Bank (PDB). However, no chitinase structure

from *Thermomyces lanuginosus* is currently available in the PDB. Therefore, the required model was constructed using the homology modeling method.

3.1.1. Homology Modeling of Chitinase

The SWISS-MODEL tool was used to predict the three-dimensional structure of the chitinase protein. The amino acid sequence of *Thermomyces lanuginosus* chitinase obtained from the NCBI database in FASTA format was used as the target sequence for constructing the homologous model. The crystal structure of *Aspergillus fumigatus* chitinase B1 (2a3c.1.A) was obtained as the best template from the SWISS-MODEL tool to build the homologous model of *Thermomyces lanuginosus* chitinase. Figure 3A shows the alignment between the target protein sequence and the template sequence used to construct the model. During modeling, the target and template sequences were aligned (Figure 3A) and the sequence of *Aspergillus fumigatus* chitinase B1 exhibited 62.28% sequence identity. Subsequently, the three-dimensional structure of the chitinase protein was constructed (Figure 3B).

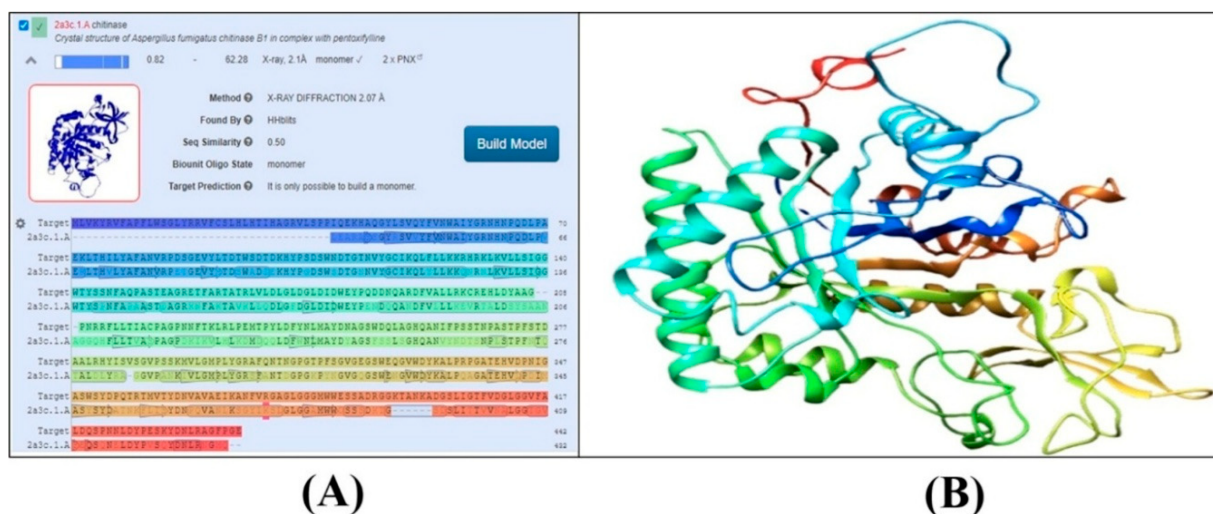


Figure 3: (A) Alignment between the target protein sequence and the template sequence used for model construction. (B) Homologous 3D chitinase model of the target protein (*Thermomyces lanuginosus* chitinase) using *Aspergillus fumigatus* chitinase B1 (PDB ID: 2A3C, chain A) as the template structure.

The modeled structure was validated using the Ramachandran plot (Figure 4). The analysis revealed that more than 90% of the amino acid residues were located in the most favored region, whereas less than 10% were present in the additionally allowed, generously allowed,

or disallowed regions. These results supported the suitability of the modeled structure for subsequent molecular docking studies. The modeled structure initially contained a bound ligand, PNX, which was removed using BIOVIA Discovery Studio [46].

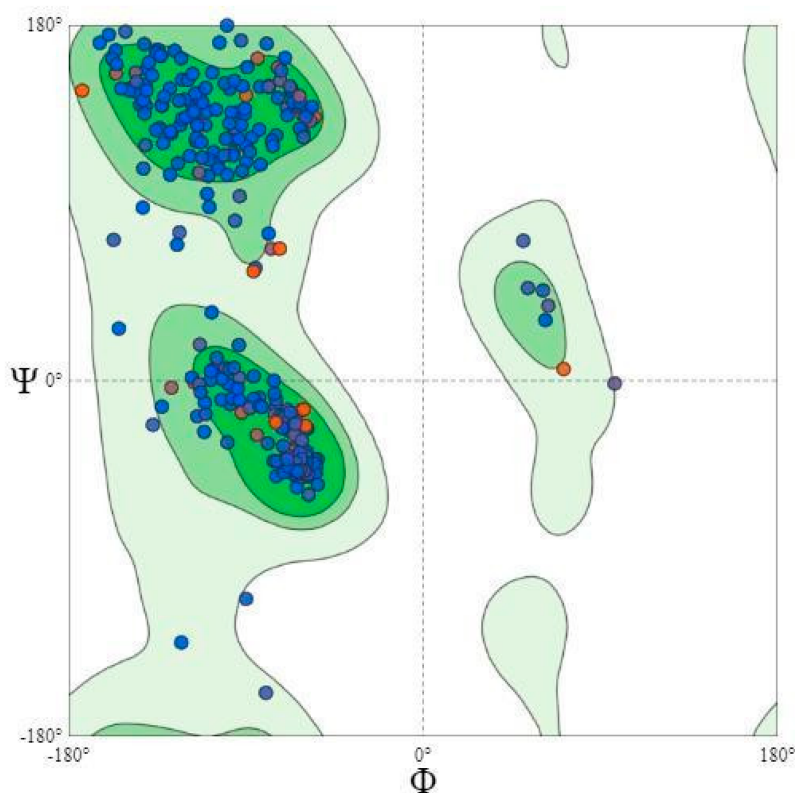


Figure 4: Ramachandran plot to validate the modeled Chitinase.

3.2. Docking of Chitinase with UDP-NAG

Locating the binding site in a specific protein is the first step before docking. The ligand can be attached to this docking site to analyze receptor-ligand interactions. The binding site in the modeled chitinase was identified using the SiteMap application, which predicts potential binding sites. The “Site Score” was used to determine the most suitable binding site among all the predicted sites [47]. A site score of ≥ 1 is considered excellent and is generally selected for subsequent docking studies. Sites with scores ranging from 0.8 to 1 may be considered partially targetable, whereas sites with scores < 0.8 are generally regarded as unsuitable for targeting. In the present study, the highest-scoring binding site in the target molecule was selected (Figure 5). Once the binding site was identified, a grid was generated around the site to define the binding region for ligand interactions during docking. Glide was used to evaluate the binding affinity of chitinase based on the docking score and Glide energy [48]. The interaction was represented by a yellow dotted line indicating the formation of a hydrogen bond. Accordingly, the ligand interaction diagrams (Figure 5) illustrate how the amino acid residues are involved in ligand binding. A more negative

docking score indicates a stronger and more favorable predicted interaction between the protein and ligand [49,50]. The docking score for this interaction was -5.568 , with a corresponding glide energy of -53.491 .

These findings suggest that chitinase may interact with UDP-NAG at the molecular level. Since UDP-NAG is associated with the glycosylation pathway [51,52], the observed favorable docking interaction may indicate the potential involvement of chitinase in modulating abnormal glycosylation processes. The hydrogen-bond interactions observed in the ligand interaction diagram further support the plausibility of the predicted binding pattern [53]. However, these observations should be interpreted cautiously, as docking analysis provides only a preliminary assessment of molecular interactions.

3.3. Protein-Protein Interaction Between Chitinase and DPAGT I

To explore the potential of chitinase in modulating abnormal glycosylation, protein-protein interaction analysis was performed between chitinase and DPAGT1, an enzyme involved in the glycosylation pathway. The ClusPro server was used for this interaction analysis. The 10 top-ranked models (Figure 6) were generated based on

balanced, hydrophobic-favored, and electrostatic-favored weighting schemes, with corresponding center and lowest energy scores (Table 1). Figure 6 presents the representative structures of the top-ranked docking clusters,

whereas the model exhibiting the lowest energy among all weighted scores was selected as the best interaction model (Figure 7).

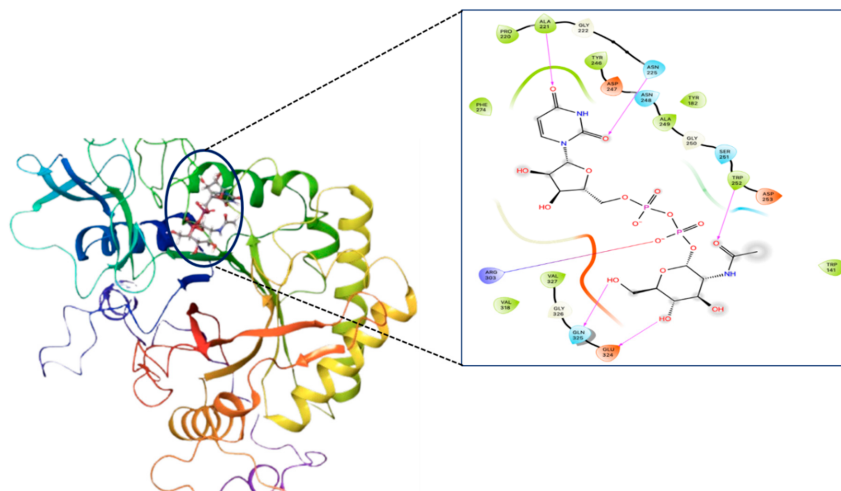


Figure 5: Molecular docking interaction between Chitinase and UDP-NAG. The microscopic view showing the ligand interaction diagram for the interaction of Chitinase and UDP-NAG.

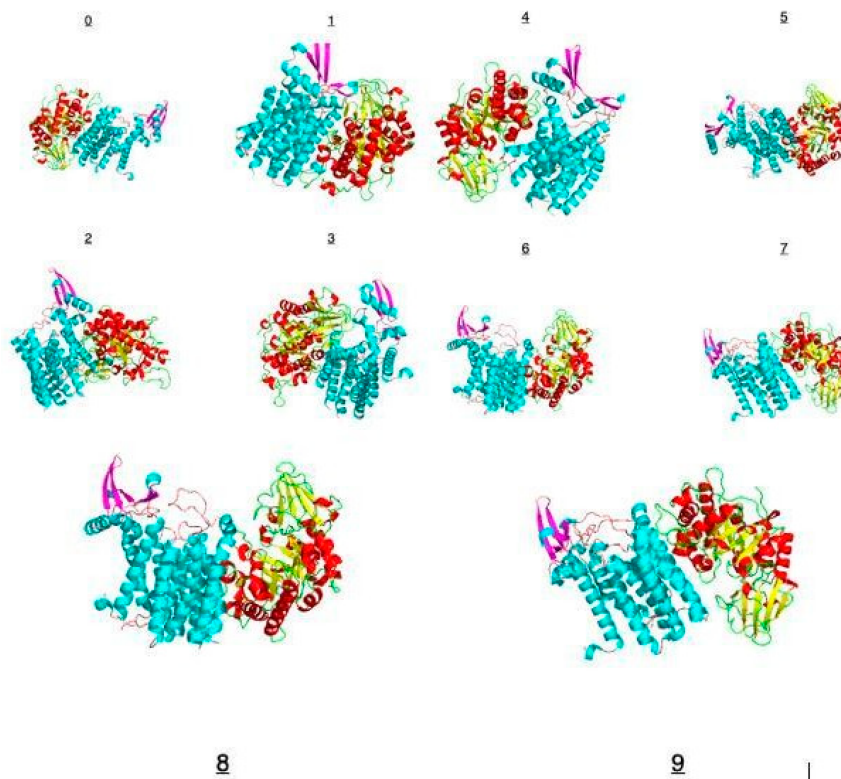


Figure 6: Generated 10 clusters of protein-protein interactions for chitinase and DPAGT. Color-coded keys depict the different components of docked protein-protein complexes. Sky blue: α helix of DPAGT1 (6FM9); Violet: β sheets of DPAGT1 (6FM9); Red: α helix of chitinase protein (2A3C.1); Yellow: β sheets of chitinase protein (2A3C.1).

Table 1: Depicting the generated clusters of protein-protein interactions the centers and lowest energy levels for balanced, electrostatic favored, and hydrophobic favored interactions.

Cluster	Representative	Balanced		Electrostatic Favored		Hydrophobic Favored	
		Members	Weighted score	Members	Weighted score	Members	Weighted score
0	Center	73	−1433.6	65	−1405.2	91	−2404.7
	Lowest Energy		−1548.4		−1541.7		−2677.1
1	Center	53	−1661.9	48	−1731.8	61	−2450.6
	Lowest Energy		−1799.9		−1845.2		−2454.0
2	Center	41	−1333.7	45	−1447.0	61	−2211.4
	Lowest Energy		−1609.1		−1510.0		−2477.8
3	Center	39	−1410.5	40	−1321.6	40	−2054.9
	Lowest Energy		−1470.3		−1612.5		−2396.5
4	Center	37	−1327.1	38	−1288.3	40	−1973.4
	Lowest Energy		−1446.0		−1483.9		−2353.4
5	Center	36	−1294.1	36	−1538.9	39	−2478.2
	Lowest Energy		−1484.4		−1538.9		−2609.2
6	Center	36	−1308.8	31	−1297.8	34	−2363.8
	Lowest Energy		−1510.4		−1502.9		−2363.8
7	Center	36	−1303.0	31	−1505.7	32	−2029.3
	Lowest Energy		−1473.3		−1505.7		−2245.6
8	Center	34	−1492.4	29	−1288.6	31	−2047.0
	Lowest Energy		−1512.4		−1452.0		−2130.9
9	Center	33	−1282.4	29	−1297.4	30	−2255.7
	Lowest Energy		−1332.7		−1462.2		−2395.7
10	Center	28	−1319.3	28	−1264.0	29	−2118.2
	Lowest Energy		−1506.5		−1445.3		−2265.1

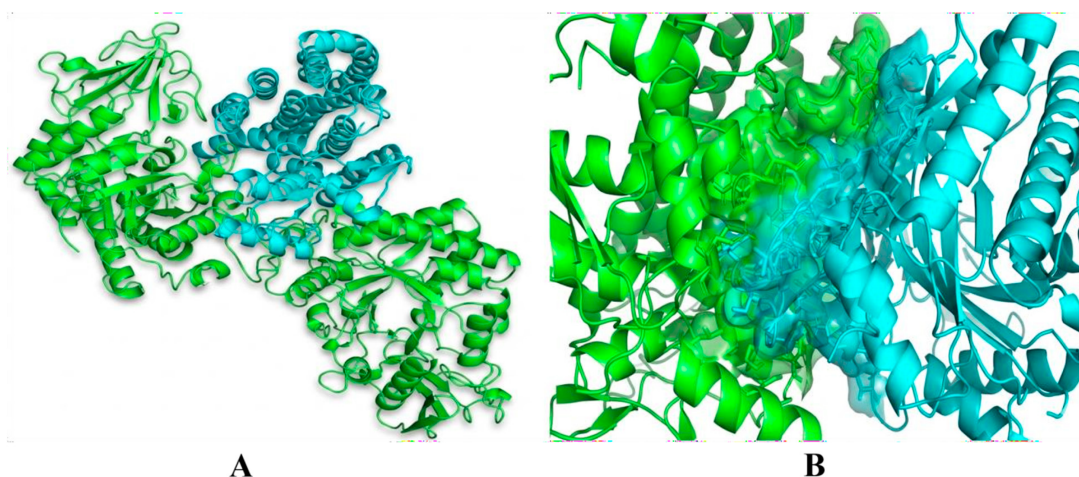


Figure 7: (A) Protein-protein docked complexes of DPAGT1 (6FM9), with chitinase protein (2A3C.1). Color-coded keys depict the different components of docked protein-protein complexes. (B) Green: Chitinase protein (2A3C.1); Sky blue: DPAGT1 (6FM9).

The observed protein-protein interaction between chitinase and DPAGT1 suggests that chitinase may interact with an enzyme directly involved in the glycosylation pathway. These findings support the proposed hypothesis that the anticancer potential of chitinase may be associated not only with its interaction with UDP-NAG but also with its potential ability to modulate DPAGT1-mediated glycosylation events. Although the interaction models obtained from ClusPro provide supportive computational evidence, these findings should be considered preliminary and require further validation through additional computational analyses and experimental studies.

Taken together, the molecular docking and protein-protein interaction analyses suggest that chitinase may influence abnormal glycosylation through interactions with both UDP-NAG and DPAGT1. Since abnormal glycosylation is closely associated with carcinogenesis and tumor progression [54], these observations provide preliminary *in silico* evidence supporting the proposed anticancer potential of chitinase. The combined findings therefore strengthen the hypothesis of the present study; however, further validation is required to confirm the mechanistic basis and biological relevance of these interactions.

The present findings are based on molecular docking and protein-protein interaction analyses performed within a single computational framework. Therefore, the observed interactions between chitinase and UDP-NAG, as well as between chitinase and DPAGT1, should be interpreted as preliminary *in silico* predictions rather than definitive evidence of stable binding.

Although the obtained docking score, Glide energy, and interaction models suggest favorable binding, further validation using alternative docking protocols, different scoring functions, appropriate control systems, molecular dynamics simulations, and experimental studies is required to confirm the robustness, stability, and biological relevance of these interactions.

4. Conclusions

Molecular docking and protein-protein interaction analyses were performed to evaluate the potential role of chitinase in modulating abnormal glycosylation. The molecular docking results were evaluated based on docking score (DS), glide score (GS), glide energy (GE), and hydrogen-bond interactions to assess the binding affinity between chitinase and the target molecule. The obtained docking score was -5.568 , and the glide energy was -53.491 , indicating favorable docking of chitinase with UDP-NAG. Ligand interaction analysis further supported the predicted binding through the formation of hydrogen bonds between the interacting molecules. In addition, the

protein-protein interaction studies generated structure and score models with balanced, electrostatic-favored, and hydrophobic-favored interactions, suggesting a favorable interaction between chitinase and DPAGT1. Taken together, these findings suggest that chitinase may modulate abnormal glycosylation through its interaction with UDP-NAG and/or the DPAGT1 enzyme, which may influence glycosylation-related processes. Therefore, chitinase may be considered a candidate for further investigation as a potential modulator of abnormal glycosylation-associated pathways. However, additional experimental studies are required to validate these *in silico* findings and to establish their mechanistic and biological significance.

List of Abbreviations

Dol-P	Dolichyl Phosphate
DS	Docking Score
DPAGT1	Dolichyl-phosphate N-acetylglucosamine phosphotransferase
FASTA	FAST-All
GE	Glide Energy
GLIDE	Grid-based Ligand Docking with Energetics
GS	Glide Score
NAG	N-acetyl-D-glucosamine
NCBI	National Center for Biotechnology Information
OPLS	Optimized Potentials for Liquid Simulations
PDB	Protein Data Bank
PNX	Pentoxifylline
RMSD	Root-Mean-Square Deviation
SP	Standard Precision
UDP	Uridine diphosphate

Author Contributions

Conceptualization: N.S., M.Y., J.S.E., and B.K.; Funding acquisition, supervision: N.S. and B.K.; Investigations: N.S., J.S.E., and M.Y.; Formal Analysis: J.S.E., B.K., and S.C.; Writing—original draft: N.S., M.Y., and B.K.; Visualization: N.S., M.Y., and B.K.; Writing—review & editing: N.S., M.Y., B.K., J.S.E., and S.C. All the authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. Protein sequences were retrieved from NCBI, ligand structures from PubChem, and protein structures from the Protein Data Bank (PDB). Homology modeling was performed using SWISS-MODEL. Publicly available software, such as “ClusPro web server,” is used.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

The authors confirm that no AI tools were used to generate any content of this manuscript.

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