ORIGINAL ARTICLE

Discovery of a Novel Peptide from *Boerhavia diffusa* Targeting Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha in Cervical Cancer: An *in Silico* Docking Study

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Abstract

Background: Therapeutic peptides and related compounds are increasingly employed to improve efficacy and specificity. A *Boerhavia diffusa* peptide targets a mutant phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene associated to cervical cancer progression. *In silico* approaches model the peptide and mutant PIK3CA sequence in 3D, and peptide–protein docking simulations uncover medicines and hydrogen bonds that may down-regulate cancer-associated proteins. Cancer informatics and structure-based drug design researchers can use protein data bank-integrative/hybrid modeling (PDB-IHM)-Model Archive structural models. **Objective:** The objective of the study was to find a peptide-based cervical cancer therapeutic that binds and down-regulates the mutant PIK3CA protein. To show *in silico* docking that the peptide and cancer-associated protein form hydrogen bonds, suggesting therapeutic potential. Provide scientists with a structural model for structure-based drug design (PDB-IHM-Model Archive). **Materials and Methods:** *B. diffusa* peptide and cervical cancer mutant *PIK3CA* gene sequences were used. The Swiss-Model Server predicted the three-dimensional structures of both sequences. Peptide–protein docking focused on intermolecular hydrogen-bond interactions to locate drugs that could bind to the predicted peptide structure. Structural simulations aid drug design studies. For cervical cancer informatics researchers, the structure was uploaded to the PDB-IHM-Model Archive (https://modelarchive.org/doi/10.5452/ma-4whza/). **Results:** This docking study indicated that the peptide directly down-regulates the altered PIK3CA protein sequence by interacting with the cancer-associated protein. The study identified hydrogen bond binding topologies that imply the peptide could downregulate and treat the mutant PIK3CA protein. A structural model and docking data were presented to help design cervical cancer drugs. **Conclusion:** *In silico* docking reveals the *B. diffusa* peptide may down-regulate the mutant PIK3CA protein, making it a promising cervical cancer treatment. Cervical cancer may be treated specifically using the peptide. This study advances the aims of sustainable development goal 3: Good health and well-being by fostering the development of novel therapeutic options for cervical cancer.

Key words: *Boerhavia diffusa,* cervical cancer, *in silico*, peptide -protein docking, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alphaw

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INTRODUCTION

A significant global public health burden is posed by uterine cervical squamous carcinoma, an infectious malignancy linked to high-risk subtypes of the human papillomavirus (HPV). Uterine cervical cancer is the fourth most frequent disease in women in terms of both incidence and mortality, with over 300,000 deaths globally in 2018.[1,2] The advent of HPV vaccines a few years ago may help to ameliorate these depressing findings in the upcoming decades.[3] But for the foreseeable future, cervical cancer will continue to be a major health concern, and there will be a need for efficient therapies, particularly as it spreads. By facilitating the creation of rationally tailored drugs, molecular research on the pathophysiology of cervical cancer holds promise for improving treatment outcomes.

Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), which encodes the alpha catalytic subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase 3, is one of the most commonly mutated oncogenes in cancer. The gene is located on the long arm of human chromosome 3 at 3q26.32. PIK3CA is a catalytic unit with a molecular weight of 110 kDa and 1068 amino acids. PIK3R1 encodes an 85 kDa regulatory component that controls it. In reaction to activating signals from receptor tyrosine kinases, the kinase phosphorylates phosphorylinositol-4, 5-bisphosphate to phosphatidylinositol-3, 4, 5-triphosphate. This phosphorylation interacts with the serine/threonine kinase AKT, the kinase complex mTORC2, and the kinase 3-phosphoinositide-dependent protein kinase 1. AKT's proximity to the other two kinases facilitates its phosphorylation.[4] This phosphorylation causes the kinase AKT to become active. AKT then phosphorylates several downstream effectors that have carcinogenic properties, either activating or inhibiting them. When engaged, the mTORC1 complex, a crucial downstream effector, stimulates protein translation and cell proliferation by blocking S6K1and EIF4EBP.[5]

Furthermore, through the actions of numerous downstream effectors, PI3K regulates other pathways associated with cancer. GSK3 phosphorylation by mTORC1 inhibits the Wnt/β-catenin pathway.[6] The inhibitory phosphorylation of tumor suppressors, including the transcription factor FOXO1, is another effect of AKT phosphorylation. Numerous malignancies, including the most common ones including breast, endometrial, and colorectal cancers, have been connected to PIK3CA mutations.[7]

About one-third of instances of estrogen receptor-positive (ER-positive), epidermal growth factor receptor 2-negative (HER2)-negative breast tumors have PIK3CA mutations, according to Martínez-Sáez *et al*. (2020). H1047, E542, E545, and N345 are the hotspot codons with the highest mutation frequencies. PIK3CA mutations have become a potential therapeutic target in metastatic ER-positive, HER2-negative breast tumors because they predict sensitivity to PI3K inhibitors.[8] After progression on Cyclin-dependent kinase inhibitor combos, the alpha-specific PI3K inhibitor alpelisib has been licensed for treatment in conjunction with hormone therapy in the metastatic setting of this subtype of breast cancer.[9] Twenty to 25% of colorectal adenocarcinomas have PIK3CA mutations. It has been suggested that their existence confers resistance to the conventional treatment for colorectal cancer, FOLFOX (5-FU, Folinic acid, Oxaliplatin).[10]

The Nyctaginaceae family includes the well-known native medicinal plant *Boerhaavia diffusa* L., which has a number of biological applications. It is also a favorite leafy green vegetable. The herb is said to have cardiotonic and antihypertensive qualities. *B. diffusa* is known to possess antibacterial, antiproliferative, antiestrogenic, immunomodulatory, hepatoprotective, antioxidant, and anticonvulsant qualities, according to pharmacological studies.[11-14]

Cervical cancer was the fourth most common cancer among women globally in 2022, with over 660,000 new cases reported annually and 350,000 fatalities. This serves as the main driving force behind the current investigation. Cervical cancer incidence and mortality are highest in low- and middle-income countries. A natural peptide-based medication can be validated using computational biology to combat the cervical cancer protein, PIK3CA. The docking data clearly indicated the peptide's direct role in the downregulation of the modified PIK3CA protein. This peptide may serve as a targeted therapy for cervical cancer, thereby advancing sustainable development goal (SDG)-3: Good health and well-being by promoting novel therapeutic approaches.

MATERIALS AND METHODS

Target sequence retrieval system

To dock with the cervical cancer protein, PIK3CA, which was obtained from the UniProt database, the peptide sequence of (*B. diffusa*) was obtained from the protein data bank/integrative/hybrid modeling (PDB-IHM (https://www.modelarchive.org/doi/10.5452/ma-4whza).

Protein 3D structure prediction

An automated homology modeling server called the Swiss Model server (https://swissmodel.expasy.org/) was used to transform the altered PIK3CA into a three-dimensional (3D) structure. To perform peptide-protein docking investigations, the peptide sequence was directly retrieved from the PDB-IHM (model-archive) database.[15] A sophisticated molecular visualization program called Discovery Studio was used to visualize the 3D structure.

Peptide-protein docking

H-Dock server (http://hdock.phys.hust.edu.cn/) was used for the docking studies. The effectiveness of our new peptide's

MPPRPSSGELWGIHLMPPRILVECLLPNGMIVTLECLREATLITIKHELFKEARKYPLH
QLLQDESSYIFVSVTQEAEREEFFDETRRLCDLRLFQPFLKVIEPVGNREEKILNREIGF
AIGMPVCEFDMVKDPEVQDFRRNILNVCKEAVDLRDLNSPHSRAMYVYPPNVESSP
ELPKHIYNKLDKGQIIVVIWVIVSPNNDKQKYTLKINHDCVPEQVIAEAIRKKTRSML
LSSEQLKLCVLEYQGKYILKVCGCDEYFLEKYPLSQYKYIRSCIMLGRMPNLMLMAK
ESLYSQLPMDCFTMPSYSRRISTATPYMNGETSTKSLWVINSALRIKILCATYVNVNIR
DIDKIYVRTGIYHGGEPLCDNVNTQRVPCSNPRWNEWLNYDIYIPDLPRAARLCLSIC
SVKGRKGAKEEHCPLAWGNINLFDYTDTLVSGKMALNLWPVPHGLEDLLNPIGVTG
SNPNKETPCLELEFDWFSSVVKFPDMSVIEEHANWSVSREAGFSYSHAGLSNRLARD
NELRENDKEQLKAISTRDPLSEITEQEKDFLWSHRHYCVTIPEILPKLLLSVKWNSRDE
VAQMYCLVKDWPPIKPEQAMELLDCNYPDPMVRGFAVRCLEKYLTDDKLSQYLIQL
VQVLKYEQYLDNLLVRFLLKKALTNQRIGHFFFWHLKSEMHNKTVSQRFGLLLESY
CRACGMYLKHLNRQVEAMEKLINLTDILKQEKKDETQKVQMKFLVEQMRRPDFMD
ALQGFLSPLNPAHQLGNLRLEECRIMSSAKRPLWLNWENPDIMSELLFQNNEIIFKNG
DDLRQDMLTLQIIRIMENIWQNQGLDLRMLPYGCLSIGDCVGLIEVVRNSHTIMQIQC
KGGLKGALQFNSHTLHQWLKDKNKGEIYDAAIDLFTRSCAGYCVATFILGIGDRHNS
NIMVKDDGQLFHIDFGHFLDHKKKKFGYKRERVPFVLTQDFLIVISKGAQECTKTRE
FERFQEMCYKAYLAIRQHANLFINLFSMMLGSGMPELQSFDDIAYIRKTLALDKTEQ
EALEYFMKQMNDAHHGGWTTKMDWIFHTIKQHALN

Figure 1: Normal amino acid sequence of the cervical cancer protein, 5-bisphosphate 3-kinase catalytic subunit alpha, retrieved from UniProt database. The normal positions, 542E and 545E, are indicated using an arrow mark



Figure 2: Normal 3D structure of the cervical cancer protein, 5-bisphosphate 3-kinase catalytic subunit alpha showing the normal amino acid positions, 542E and 545E, viewed using Discovery Studio software

binding score signifies a favorable interaction between a ligand and its target protein within molecular docking and drug development, especially when using algorithms like AutoDock Vina. More negative values usually signify stronger binding, pointing to a more stable and likely interaction.

The UniProt database was used to choose the mutant and normal amino acid sequences of PIK3CA (P42336) [Figures 1-3] and our peptide (ma-4whza) [Figures 4 and 5] for peptide-protein docking studies.[17] Figures 4

MPPRPSSGELWGIHLMPPRILVECLLPNGMIVTLECLREATLITIKHELFKEARKYPLH
QLLQDESSYIFVSVTQEAEREEFFDETRRLCDLRLFQPFLKVIEPVGNREEKILNREIGF
AIGMPVCEFDMVKDPEVQDFRRNILNVCKEAVDLRDLNSPHSRAMYVYPPNVESSP
ELPKHIYNKLDKGQIIVVIWVIVSPNNDKQKYTLKINHDCVPEQVIAEAIRKKTRSML
LSSEQLKLCVLEYQGKYILKVCGCDEYFLEKYPLSQYKYIRSCIMLGRMPNLMLMAK
ESLYSQLPMDCFTMPSYSRRISTATPYMNGETSTKSLWVINSALRIKILCATYVNVNIR
DIDKIYVRTGIYHGGEPLCDNVNTQRVPCSNPRWNEWLNYDIYIPDLPRAARLCLSIC
SVKGRKGAKEEHCPLAWGNINLFDYTDTLVSGKMALNLWPVPHGLEDLLNPIGVTG
SNPNKETPCLELEFDWFSSVVKFPDMSVIEEHANWSVSREAGFSYSHAGLSNRLARD
NELRENDKEQLKAISTRDPLSKITKQEKDFLWSHRHYCVTIPEILPKLLLSVKWNSRD
EVAQMYCLVKDWPPIKPEQAMELLDCNYPDPMVRGFAVRCLEKYLTDDKLSQYLIQ
LVQVLKYEQYLDNLLVRFLLKKALTNQRIGHFFFWHLKSEMHNKTVSQRFGLLLES
YCRACGMYLKHLNRQVEAMEKLINLTDILKQEKKDETQKVQMKFLVEQMRRPDFM
DALQGFLSPLNPAHQLGNLRLEECRIMSSAKRPLWLNWENPDIMSELLFQNNEIIFKN
GDDLRQDMLTLQIIRIMENIWQNQGLDLRMLPYGCLSIGDCVGLIEVVRNSHTIMQIQ
CKGGLKGALQFNSHTLHQWLKDKNKGEIYDAAIDLFTRSCAGYCVATFILGIGDRHN
SNIMVKDDGQLFHIDFGHFLDHKKKKFGYKRERV
PFVLTQDFLIVISKGAQECTKTREFERFQEMCYKAYLAIRQHANLFINLFSMMLGSGM
PELQSFDDIAYIRKTLALDKTEQEALEYFMKQMNDAHHGGWTTKMDWIFHTIKQHA
LN

Figure 3: Mutated amino acid sequence of the cervical cancer protein, 5-bisphosphate 3-kinase catalytic subunit alpha, retrieved from UniProt database. The mutated positions, 542K and 545K, are indicated using an arrow mark

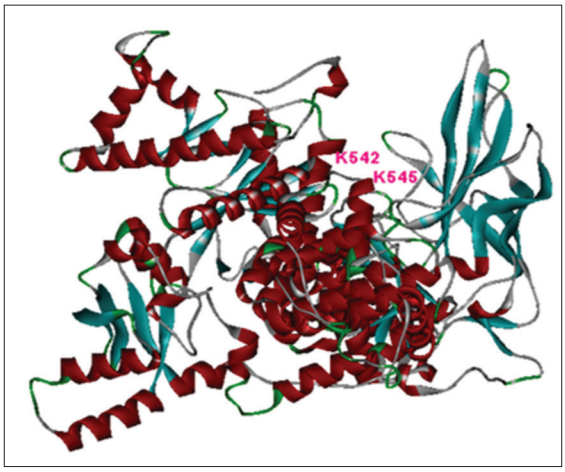


Figure 4: Altered 3D configuration of the Cervical Cancer protein, PIK3CA, displaying the mutated amino acid locations, 542K and 545K, observed through Discovery Studio software.

Table 1: Drug docking summary (PIK3CA -3D novel peptide)

Target protein	Test compound
PK3CA (Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform)	3D novel peptide
P42336 PK3CA_HUMAN	–321.45 kcal/mol

PIK3CA: Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha

binding to the Cervical Cancer protein PIK3CA was evaluated using the scoring function.[16]

RESULTS AND DISCUSSION

Table 1 represents the binding score achieved from docking the peptide with PIK3CA via the H-Dock server. A greater negative binding score signifies improved binding affinity. A negative

SFQALLERIYFHVKIEYLVKVLTKNCRIILWLFKDPFTHYIRYQGKSILS

Figure 5: Novel peptide sequence derived from *Boerhavia diffusa* retrieved from the model archive database. The peptide sequence length is 50 aa

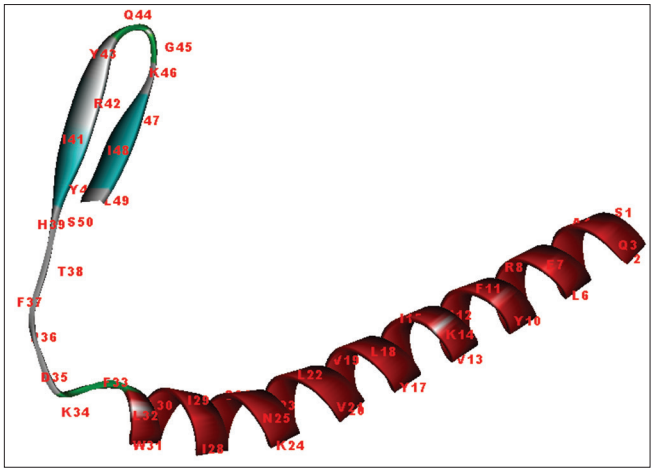


Figure 6: Altered 3D configuration of the cervical cancer protein, 5-bisphosphate 3-kinase catalytic subunit alpha, displaying the mutated amino acid locations, 542K and 545K, observed through Discovery Studio software

and 5 display the peptide sequence together with the corresponding 3D structure. The 3D structure for peptide-protein docking studies was modeled using the SWISS MODEL server 25 [Figures 2,3,6]. A service for automated comparative modeling of 3D protein structures is called SWISS-MODEL (http://swissmodel.expasy.org). It has led the way in automated modeling since 1993 and is today the most widely used free web application. In 2002, the service handled 120,000 user queries for 3D protein models. The WWW interface of SWISS-MODEL allows for varying degrees of user participation. 3D protein structures can be used to efficiently design experiments such as site-directed mutagenesis, investigations of disease-related mutations, or the structure-based design of specific inhibitors. These structures also provide crucial information about the molecular basis of protein action.[18]

Berman *et al*. conducted peptide-protein docking investigations using the H-Dock service. To make efficient use of the homologous complexes available in the PDB, they developed a hybrid docking technique that automatically incorporates binding interface information into traditional global docking. Although their iterative knowledge-based scoring function contributed to their success,[19] their algorithm has been among the top-performing groups in recent common agricultural policy regionalized impact (CAPRI) sessions using the interface information. Because of the strong performance of their docking algorithm, they developed the HDOCK server, a comprehensive framework for protein–protein and protein–DNA/RNA docking, similar to our hybrid docking pipeline used for CAPRI. HDOCK uses intrinsic scoring methods for protein–protein and protein–DNA/RNA docking. Users can examine the results interactively on a web page and receive an email notification if they provide a functional email address. The entire docking process is automated.

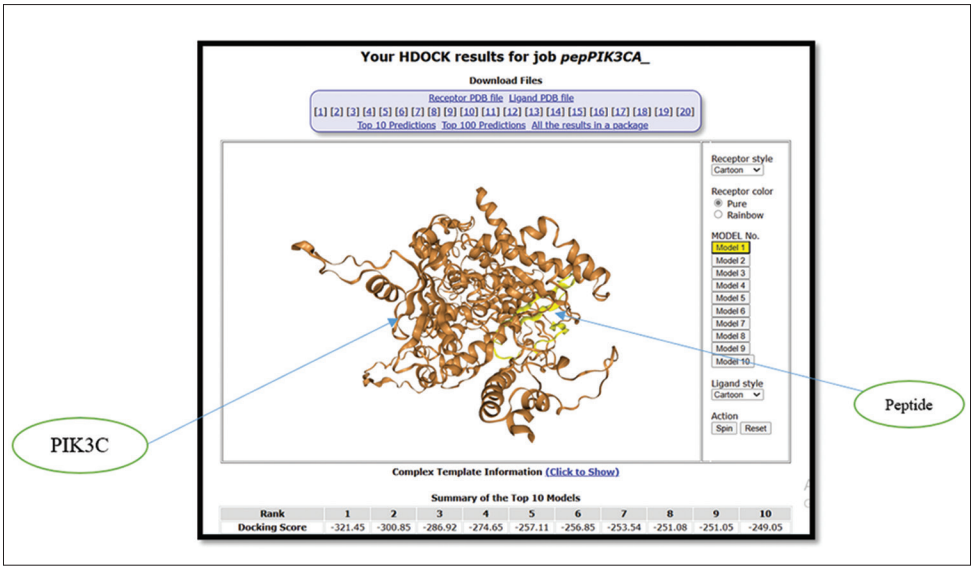


Figure 7: H-Dock outcomes displaying the intricate structure of the peptide bound to the 5-bisphosphate 3-kinase catalytic subunit alpha protein, along with corresponding binding scores. The lowest binding score is –321.45 kcal/mol. Binding affinity refers to the extent of interaction between a ligand and its target protein at the binding site. A larger negative binding affinity value signifies that the ligand can attach more strongly to the target protein

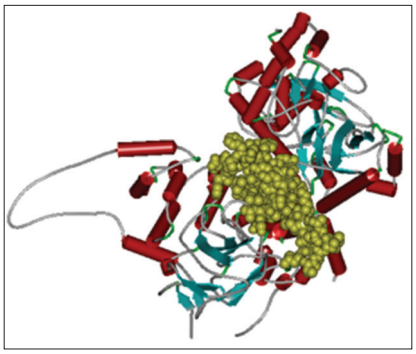


Figure 8: 3D complex form of the peptide with 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) viewed using Discovery Studio software. The yellow-colored structure indicates the peptide that is bound to the functional domain cavities of PIK3CA. Peptides and peptidomimetics are important because they offer a rational approach to understanding biological processes and to the development of novel medications, biomaterials, catalysts, or semiconductors

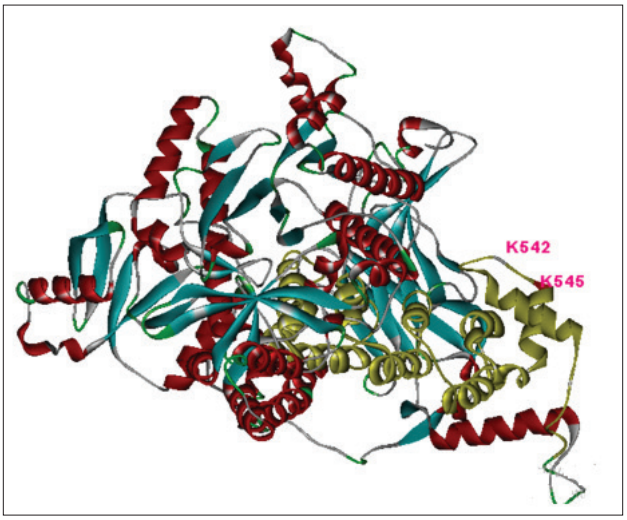


Figure 9: Three-dimensional arrangement of 5-bisphosphate 3-kinase catalytic subunit alpha. The yellow structure highlights the functional domain regions, including the two distinct mutated sites, 542K and 545K, marked in pink. Super secondary structures, referred to as motifs, are specific configurations of secondary structures like beta strands and alpha helices that serve multiple purposes, including creating binding sites and providing stability. Arrangements of patterns referred to as domains can independently fold and extend the peptide backbone

The binding score between the peptide and PIK3CA was −321.45 kcal/mol, which was adversely higher [Figure 7]. The binding scores reflecting the effectiveness of the 3D peptide-protein interaction are clearly shown in Figures 8-12. The novel modeled peptide's binding interaction scores with the cervical cancer protein PIK3CA are displayed in Table 1. The amino acids implicated in H-bond and electrostatic interactions were thoroughly analyzed utilizing the docked model and Discovery Studio software. In drug docking research, predicting the functional domain is an essential step.[20] Several researchers have demonstrated their docking capabilities using the H-Dock server.

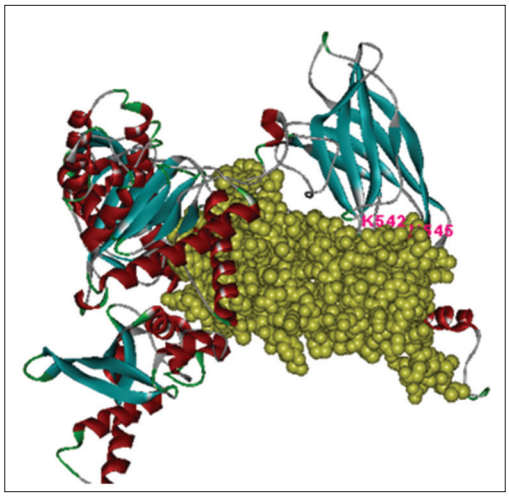


Figure 10: 3D complex structure of 5-bisphosphate 3-kinase catalytic subunit alpha (ribbon model) with the peptide (CPK model). The yellow colored structure shows the functional domain ranges encompassing the two different mutated sites, 542K and 545K, indicated in pink color. The above picture clearly shows that the binding regions lie inside the domain region and encompasses the mutated sites. Important results in signal transduction and a variety of healthy physiological and disease-related processes are attributed to protein interaction domains (PIDs). Finding new treatments may be facilitated by targeting these PIDs with peptides and small compounds that can alter their networks of interactions

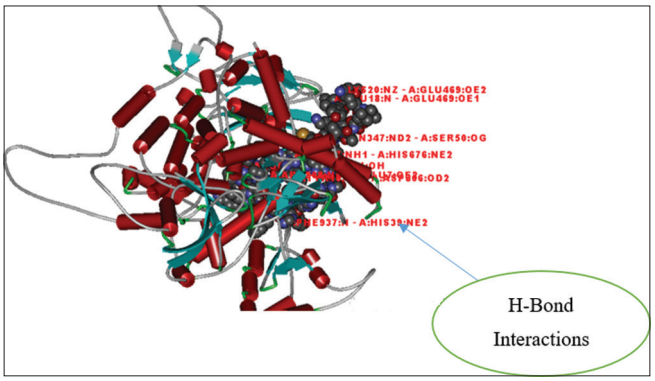


Figure 11: 3D H-bond interaction between the peptide and 5-bisphosphate 3-kinase catalytic subunit alpha protein, showing the respective amino acids present at the binding regions with the binding positions. One particular kind of dipole-dipole attraction between molecules is hydrogen bonding. It is stronger than van der Waals forces but weaker than covalent or ionic bonds

Remarkably, we discovered that the newly identified peptide binds directly to functional domains of the PIK3CA cervical cancer protein. The H-Bond interacting amino acids are follows: ASN:347, SER:50, ARG:808, GLU:7, PHE:937, HIS:39, ARG:8, TYR:641, TYR:10, ASP:806, LEU:18, GLU:469, LYS:20, GLU:469, LYS:20, GLU:469, ARG:27, HIS:676.

The three functional domains of PIK3CA are as follows: 16–105: PS51544 (Phosphatidylinositol 3-kinase adaptor-binding); 330–487: PS51547 (C2 phosphatidylinositol

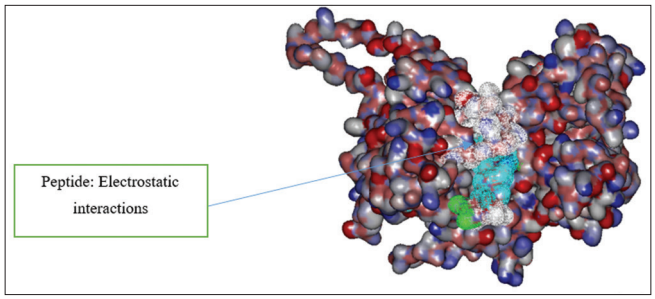


Figure 12: Binding of the peptide with 5-bisphosphate 3-kinase catalytic subunit alpha protein using 3D Electrostatic interaction viewed using Discovery Studio software. The primary mechanism of adsorption of ionic and ionizable organic compounds is electrostatic interaction, which includes electrostatic attraction and repulsion and is fundamental to the formation of ionic bonds. Usually, the opposing charge of the adsorbent surface attracts these organic molecules

3-kinase); 517–694: PS51545 (Phosphatidylinositol kinase (PIK) helical domain); and 765–952: PS50290 (Phosphatidylinositol 3- and 4-kinases catalytic domain). The novel peptide interacts with these functional domains. We discovered that the functional domain areas where the peptide interacts contain the altered locations, E542K and E545K [Figures 5,7-9]. Based on the docking score determined by the H-Dock server approach, all of the data unequivocally demonstrated that the new peptide effectively inhibited the cervical cancer protein, PIK3CA.

CONCLUSION

The latest therapeutic strategies for efficient molecular drug delivery employ peptides. Peptides are frequently employed in therapeutic processes to optimize the therapeutic effects of drugs or related compounds. Here, this work unequivocally demonstrates that the distinct natural peptide sequence is inhibited by the derived cervical cancer protein PIK3CA. The peptide's pharmacological effects on the *PIK3CA* gene, which is associated with an individual's susceptibility to cervical cancer, can thus be shown. In the end, we determine that the de novo peptide, a naturally occurring test peptide obtained from *B. diffusa*, is a successful medication for treating cervical cancer. To help combat cancer, our structure has been added to the PDB-IHM (https://modelarchive.org/doi/10.5452/ma-4whza). Docking showed that the peptide directly downregulated the mutated PIK3CA protein. The identified peptide may serve as a targeted cervical cancer treatment, advancing SDG 3: Good Health and Well-Being through precision medicine and SDG 9: Industry, Innovation, and Infrastructure through computational drug discovery.

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