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Homology Modeling and Structure Based Drug Design for Human Gastric Cancer

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Abstract: *This research article delves into the multifaceted world of structural biology and bioinformatics, exploring a diverse array of tools and resources employed to decipher the intricacies of proteins and their implications in health and disease. The paper navigates through various computational tools and databases used for sequence analysis, structural analysis, mutation site detection, and molecular docking, shedding light on their individual contributions in unraveling the secrets of proteins. COBALT serves as the initial compass, guiding researchers in the alignment of protein sequences, identifying conserved domains, and elucidating structural features in proteins. The exploration continues, with a focus on tools such as RasMol, PyMol, and Pharmit. This research article explores a range of bioinformatics tools and databases crucial for elucidating the complex world of proteins and their involvement in diseases like gastric cancer. It begins by highlighting the pivotal role of the Catalogue of Somatic Mutations in Cancer (COSMIC) in mutation site detection, providing a comprehensive repository of somatic mutations in cancer. The Kyoto Encyclopedia of Genes and Genomes (KEGG) complements this with a wealth of biological data and pathways. Shifting the focus to protein stability and dynamics, the article introduces DynaMUT, a computational tool employing molecular dynamics simulations to predict mutation impacts on protein behavior. Lastly, SwissDock takes the stage for drug discovery, facilitating the prediction and analysis of interactions between small molecules and target proteins. Collectively, these tools and databases offer an interdisciplinary lens through which researchers unravel protein intricacies and their relevance in diseases, exemplifying the indispensable role of structural biology and bioinformatics in advancing biological understanding.*

Keywords: *Gastric Cancer; Molecular Docking; COSMIC; PyMol; RasMol; SwissDock; DynaMut*

I. INTRODUCTION

The structure of recombinant human gastric lipase (rHGL) includes a core domain and a "cap" domain. It possesses a classical catalytic triad and N-glycosylation sites. HGL plays a crucial role in newborns, as pancreatic lipase is not fully developed in infants, and it initiates the digestion of dietary fats. Gastric lipase and other preduodenal lipases are resistant to acidic conditions and can assist in fat digestion in the stomach and duodenum. Human lysosomal acid lipase (HLAL) is similar in sequence to HGL but has different enzymatic activities, including the hydrolysis of triglycerides and cholesteryl esters. Mutations in the LIPA gene (Lysosomal Acid Lipase A gene), which encodes HLAL, can lead to genetic disorders like Wolman disease and cholesteryl ester storage disease. Recombinant HGL is produced using the baculovirus/insect cell system and has high specific activity. Crystals of rHGL are obtained and analyzed for their structure, revealing specific characteristics. The catalytic activity of rHGL is tested both in dissolved and intact crystals, with specific activity measured. In situ catalytic activity is assessed by incubating a single rHGL crystal in a substrate solution, resulting in coloration [1]. HGL is an enzyme secreted by the stomach that remains stable and active in the highly acidic environment of the stomach. It plays a significant role in the digestion of dietary fats, contributing to approximately 30% of the fat digestion processes in humans. HGL is described as a globular protein belonging to the α/β hydrolase fold family. Its catalytic serine is located deep within the enzyme and is covered by a domain known as the "extrusion domain." This extrusion domain comprises a "cap" domain and a segment consisting of 58 residues referred to as the "lid". The exact roles played by the cap and lid domains during the catalytic process of HGL have not been fully understood. To investigate these roles, the crystal structure of the open form of dog gastric lipase (DGL) in complex with a covalent inhibitor was solved. The inhibitor and detergent molecules were used to mimic a triglyceride substrate, interacting with residues from both the cap and lid domains [2]. Gastric cancer, also known as stomach cancer, remains a significant global health concern, accounting for a substantial portion of cancer-related morbidity and mortality. It poses a particularly formidable challenge due to its often asymptomatic early stages and the limited effectiveness of current therapeutic options. As such, the exploration of novel treatment strategies, including structure-based drug design, has garnered increasing attention in the quest to combat this disease.

One of the critical aspects of developing targeted therapies for gastric cancer involves understanding the molecular structures and interactions of proteins associated with the disease. In this context, homology modeling and structure-based drug design play pivotal roles. Homology modeling, a computational technique, enables the prediction of protein structures based on the known structures of homologous proteins. This method has proven invaluable in elucidating the three-dimensional architecture of biologically significant proteins, including those implicated in gastric cancer. Human gastric lipase (HGL) is one such protein that has emerged as a potential target for the development of novel therapeutic interventions in gastric cancer. Gastric lipase, primarily associated with lipid digestion in the stomach, has been found to have diverse biological roles, including implications in tumor progression and cancer metabolism. Understanding the structural characteristics of human gastric lipase (HGL) and its potential druggable sites is essential for the rational design of targeted therapies aimed at mitigating the effects of gastric cancer [3,4,5].

Gastric cancer is a global health concern characterized by its high prevalence, particularly in certain regions such as East Asia, South America, and parts of Eastern Europe. It ranks as the fifth most common cancer worldwide and the third leading cause of cancer-related mortality, making it a significant public health issue [6]. Gastric cancer exhibits marked geographic and demographic variations in its incidence rates. Understanding these variations and the associated risk factors, including *Helicobacter pylori* infection, dietary habits, and genetic predisposition, is crucial in developing effective prevention and treatment strategies. The Tripartite Motif (TRIM) family of proteins, encoded by TRIM genes, is known for their role in various human diseases, including cancer. TRIM16 is one such protein, with tumor suppressive properties. TRIM16 is associated with the retinoid signaling pathway, which plays a role in cancer cell death. Overexpression of TRIM16 has been linked to decreased cell growth, motility, and tumorigenicity in various cancers [7]. *Helicobacter pylori* infection is a well-established risk factor for gastric cancer. This bacterium colonizes the stomach lining and can lead to chronic gastritis, peptic ulcers, and eventually, in some cases, gastric cancer. Understanding the molecular mechanisms by which *H. pylori* promotes carcinogenesis, such as through the activation of inflammatory pathways and the disruption of gastric epithelial homeostasis, is crucial for developing preventive strategies and targeted therapies [8]. The asymptomatic nature of early-stage gastric cancer and the lack of highly sensitive screening tools pose significant diagnostic challenges. Consequently, gastric cancer often goes undetected until it reaches an advanced stage, limiting treatment options and reducing overall survival rates. Proteins are key players in cellular functions, and alterations in their structure and function are often associated with cancer initiation and progression. Mutations, overexpression, or dysregulation of specific proteins can contribute to carcinogenesis. Determining the three-dimensional structures of proteins involved in gastric cancer provides crucial insights into their mechanisms of action. Structural data can reveal active sites, binding pockets, and potential druggable regions, aiding in the rational design of targeted therapies. Homology modeling relies on the premise that evolutionarily related proteins share structural similarities. This technique involves sequence alignment, template selection, and model building, ultimately resulting in a predicted protein structure. The advent of precision medicine allows for the tailoring of treatments to the genetic and molecular profiles of individual patients. Targeted therapies designed using protein structures offer the potential for more effective and less toxic interventions. While personalized medicine holds great promise, there are challenges to overcome, including the identification of appropriate biomarkers and the development of novel therapeutics [9,10,11,12].

II. MATERIAL AND METHODS

For the sequence analysis of protein COBALT has been used. COBALT is a bioinformatics tool developed by the National Center for Biotechnology Information (NCBI) for the alignment of protein sequences. It is primarily used for identifying and comparing conserved domains and structural features in proteins. Cobalt is a part of the broader suite of tools and resources offered by NCBI to help researchers analyze and interpret biological data. Cobalt is designed to align protein sequences. It can be used to identify regions of similarity or conservation among a set of protein sequences, which is critical for understanding the relationships between different proteins and their functional domains [13,14].

For structural analysis of protein RasMol, PyMol, Pharmit has been used. RasMol is an early molecular visualization software tool that has been widely used in the field of structural biology and biochemistry. It was first developed in the early 1990s by Roger Sayle and has been instrumental in the exploration of protein and nucleic acid structures [15,16]. PyMOL is a more modern and versatile molecular visualization tool that has gained popularity in the field of structural biology. It was created by Warren L. DeLano and is known for its user-friendly graphical user interface and scripting capabilities. PyMOL provides high-quality molecular rendering with advanced graphics capabilities, allowing users to create visually appealing images and animations of molecular structures [17,18]. Pharmit is a molecular docking and virtual screening tool used for the computational analysis of protein-ligand interactions.

The red color is showing the helices in the protein. There are 3053 helix structure present in the protein.

The alpha-helix is a common secondary structure motif in proteins. Knowing how it forms and stabilizes allows researchers to understand the principles of protein folding. This knowledge is essential in the design of stable and functional proteins, including enzymes and therapeutic proteins.

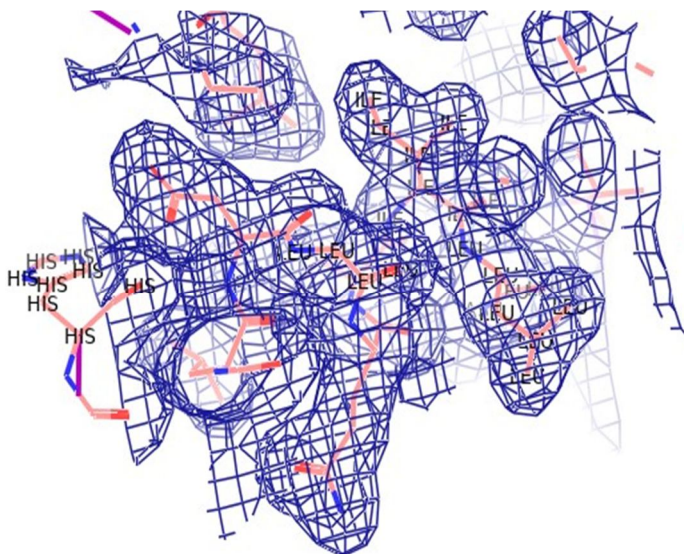


FIGURE 3: VISUALIZATION OF ROVING DENSITY TO SHOW ACTIVE SITE OF ATOM IN PYMOL

Understanding the active site helps elucidate a protein's function. It provides insights into the specific substrates or ligands that bind to the protein and the chemical reactions it catalyzes. In computer-aided drug design, molecular docking and virtual screening are used to predict the binding of small molecules to a protein's active site. Knowing the active site's properties and structure is essential for these computational techniques, which aid in drug discovery.

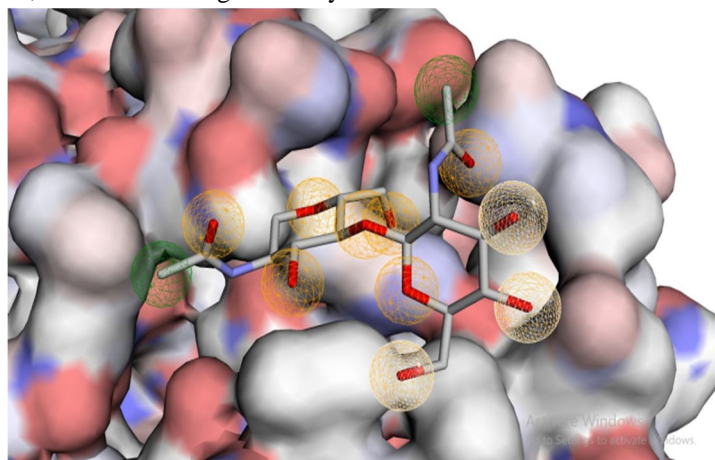
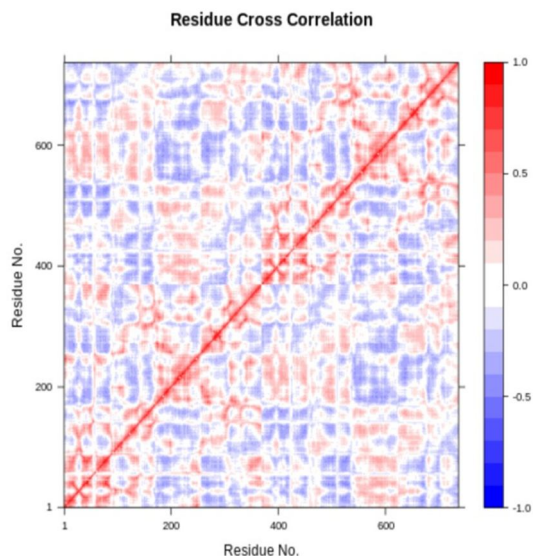


FIGURE 4: PHARMIT RESULT

Green rounds are showing hydrophobic ends, dark yellow rounds are showing hydrogen acceptor and light yellow rounds are showing hydrogen donor.

Knowledge of hydrogen acceptors and donors is crucial for understanding the interaction between proteins and ligands, including small molecules and other proteins. These interactions are critical for drug design and the development of therapeutic agents. In structure-based drug design and virtual screening, identifying hydrogen bonding sites in target proteins is essential. It aids in the identification of compounds that can form key hydrogen bonds with the protein's active site, leading to more effective drug candidates.



The residue cross-correlation was determined using all available modes.

- A correlation map that shows parts of the protein structure that are correlated (red) and anti-correlated (blue).
- Under the premise that C_{ab} = Correlation between Residues A and B
- If C_{ab} is equal to 1, then the fluctuations of residues A and B are totally correlated (same period, same phase), while if C_{ab} is equal to -1, then the fluctuations of residues A and B are completely anticorrelated (same period, opposite phase), and if C_{ab} is equal to 0, then the fluctuations of a and b are not correlated.
- If C_{ab} is equal to 1, then the fluctuations of residues A and B are totally correlated (same period, same phase), while if C_{ab} is equal to -1, then the fluctuations of residues A and B are completely anticorrelated (same period, opposite phase), and if C_{ab} is equal to 0, then the fluctuations of a and b are not correlated.

Figure 5: DynaMut result (Dynamical Cross-Correlation Map)

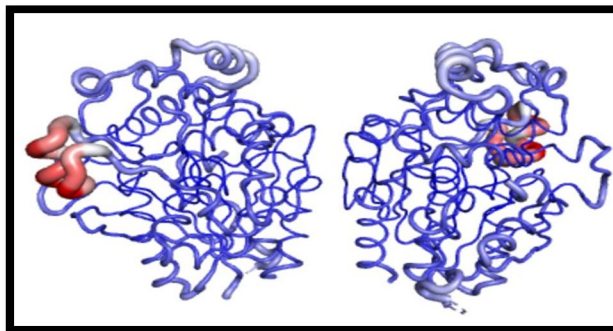
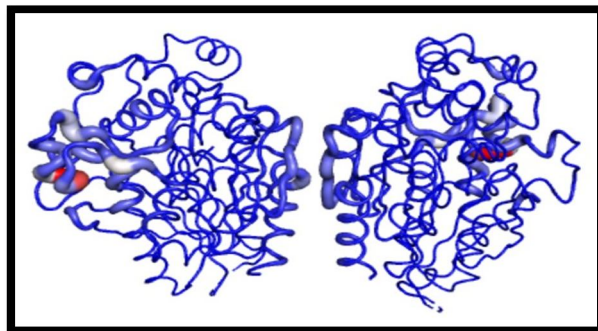


Figure 6: DynaMut result showing deformation of protein Figure 7: DynaMut result showing Atomic fluctuation of protein

The magnitude of the deformation/fluctuation is represented by thin to thick tube colored blue (low), white (moderate) and red (high). Knowing how a protein fluctuates and deforms is crucial for understanding its function and interactions. The representation helps in assessing the stability of a protein or complex. Proteins with low fluctuations (blue) may be more stable, while those with high fluctuations (red) may be less stable or prone to structural changes. Understanding fluctuations can provide insights into the functional properties of proteins. Changes in protein dynamics can affect binding affinities, enzymatic activities, and other functional aspects.

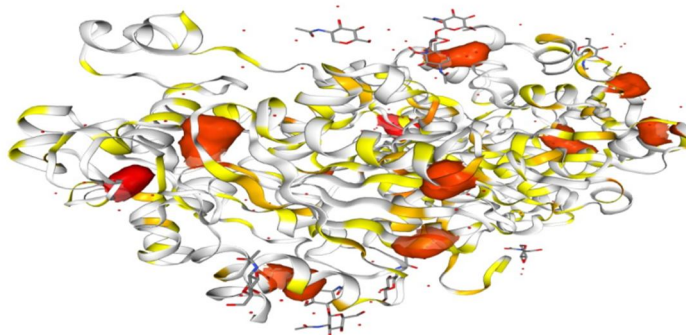


FIGURE 8: VISUALIZING THE OLIGOMERIZATION AND MUTATION IN 1HLG PROTEIN USING COSMIC3D

Visualizing oligomerization, where multiple protein subunits come together to form a complex, can provide insights into the functional significance of protein assemblies. It helps researchers comprehend how the protein functions in its natural context, which is crucial for understanding its biological roles. Visualization of mutations and their effects on protein structure is essential for rational drug design. It allows researchers to identify potential drug targets and design small molecules or biologics that can interact with the mutant protein to restore normal function or inhibit disease-related activities.

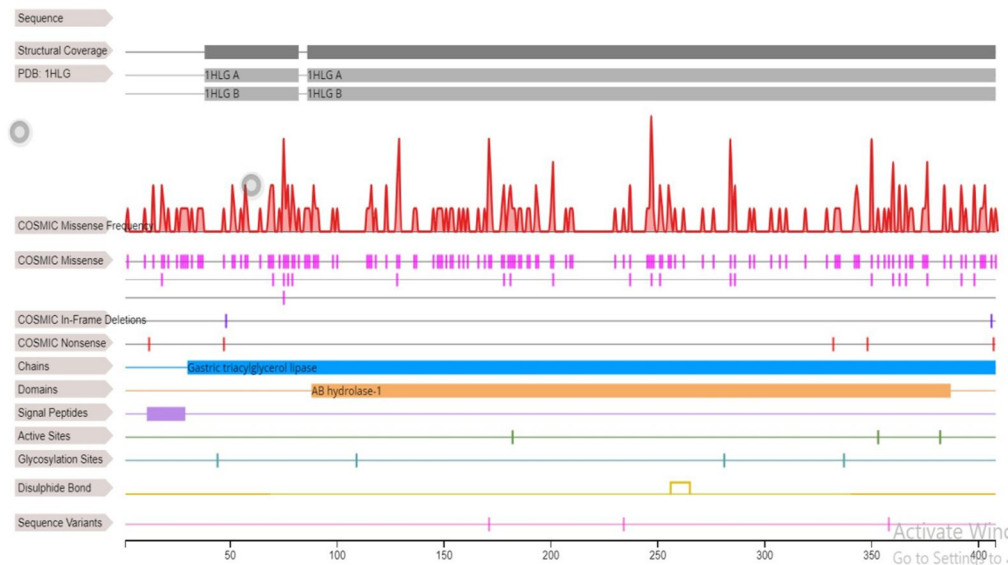


FIGURE 9: MISSENSE MUTATION FREQUENCY IN THE 1HLG IN THE GASTRIC CANCER (obtained through COSMIC)

Highest missense mutation frequency showed in the position 75, 128, 171, 247, 284 and 350.

When the translation of a protein includes a different amino acid as a result of a single nucleotide change in the DNA, this sort of genetic mutation is known as a missense mutation. This type of mutation can affect how a protein behaves in a variety of ways, depending on the position and type of the altered amino acid. Conservative and non-conservative missense mutations are typically separated. A conservative missense mutation is one where the amino acid is changed to an amino acid with a comparable chemical composition.

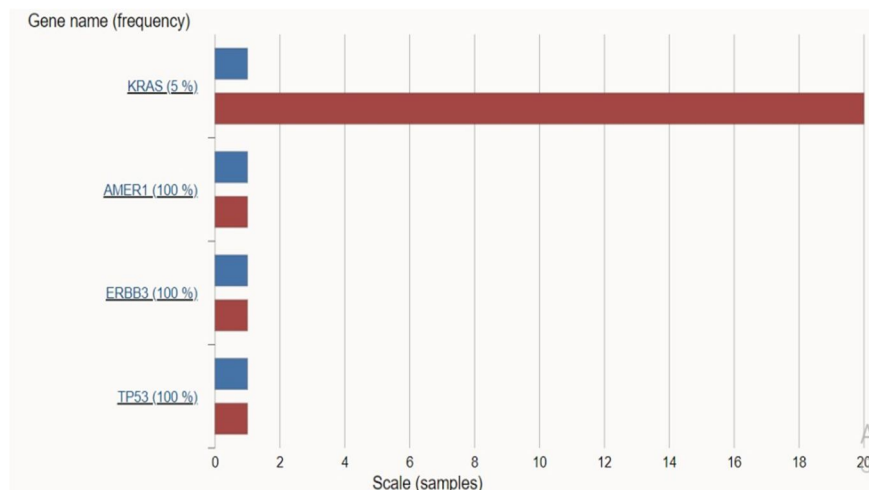


FIGURE 10: FIND TOP MUTATED GENE IN THE GASTRIC CANCER THROUGH COSMIC

The top mutated genes find from COSMIC are KRAS, AMER1, ERBB3 and TP53. KRAS is the most mutated gene in the gastric cancer. Further, utilizing KEGG database, the mutation pathway for KRAS has been visualized.

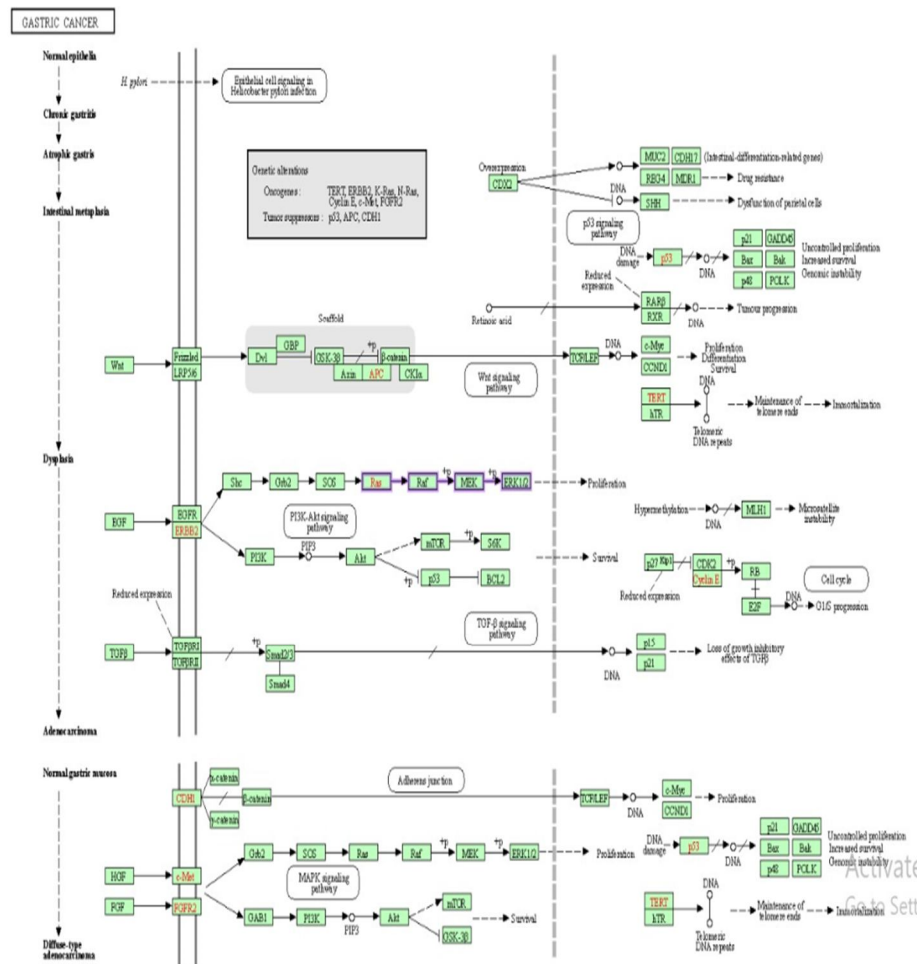


FIGURE 11: KRAS GENE MUTATION PATHWAY IN GASTRIC CANCER THROUGH KEGG

In cancer research and treatment, understanding the mutation pathway of cancer cells is vital. It allows for the development of targeted therapies that specifically address the genetic abnormalities responsible for the disease, leading to more effective and less toxic treatments. In drug discovery, knowledge of mutation pathways can aid in identifying drug targets. It helps researchers understand which proteins or pathways are altered in a disease, providing valuable information for the development of new drugs or the repurposing of existing ones.

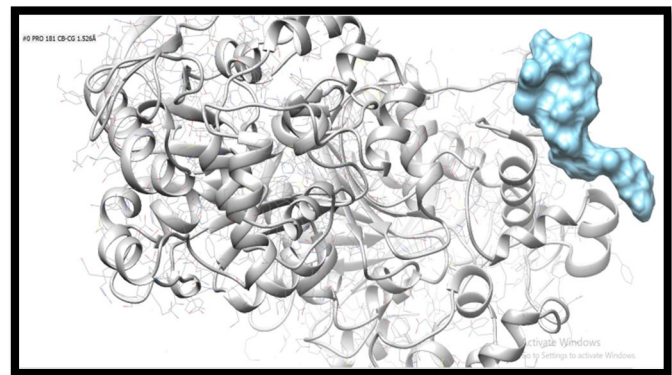
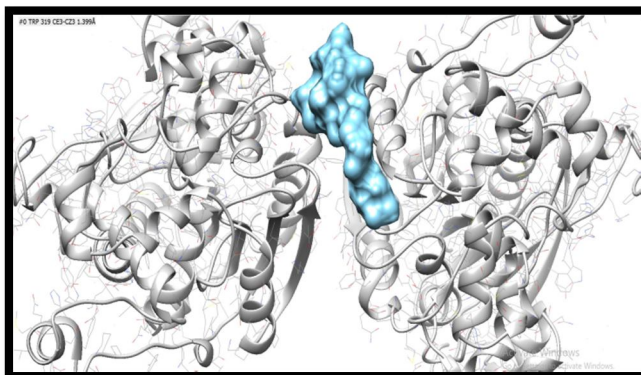


FIGURE 12: Docked image of protein with Trastuzumab Emtansine FIGURE 13: Docked image of protein with Sunitinib

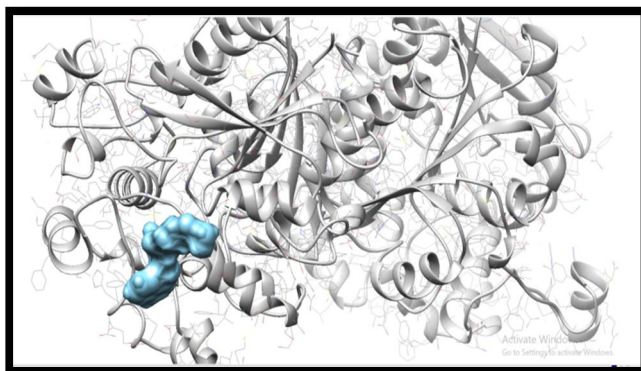


FIGURE 14: Docked image of protein with Olaparib

TABLE 1: DOCKING RESULT

Drug	Pubchem Id	Binding Energy(kcal/mol)	Interacting residue
TrastuzumabEmtansine	166596981	-8.53	First pocket
Sunitinib	5329102	-7.44	Second pocket
Olaparib	23725625	-8.27	Second pocket

TrastuzumabEmtansine, Sunitinib, and Olaparib are three important drugs that have significant roles in various aspects of cancer treatment and targeted therapy. TrastuzumabEmtansine is an antibody-drug conjugate used in the treatment of HER2-positive breast cancer. Sunitinib is a tyrosine kinase inhibitor employed in the management of advanced kidney cancer, gastrointestinal stromal tumors (GISTs), and other malignancies. Olaparib is a PARP inhibitor used in the treatment of ovarian and breast cancers, particularly those associated with BRCA mutations. TrastuzumabEmtansine, often referred to as T-DM1, is an antibody-drug conjugate. It combines the monoclonal antibody trastuzumab with the cytotoxic agent DM1 (emtansine). Trastuzumab targets the HER2 receptor, which is overexpressed in some breast cancers, while DM1 is a potent chemotherapy agent. Sunitinib is a tyrosine kinase inhibitor (TKI) that interferes with the signaling pathways involved in cell proliferation and angiogenesis. It targets multiple receptor tyrosine kinases, including those involved in vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) signalling. Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. It interferes with the repair of DNA in cancer cells, particularly those with BRCA mutations. By inhibiting PARP, Olaparib prevents the repair of DNA damage, leading to the death of cancer cells.

The utilization of these drugs could be explored in the framework of structure-based drug design and personalized medicine for gastric cancer. Their interactions with specific protein targets or mutation profiles may play a critical role in developing novel therapeutic interventions.

IV. CONCLUSION

In conclusion, this research article offers a comprehensive exploration of the tools, databases, and drugs that collectively form the foundation for understanding the intricate world of proteins and their implications in the context of gastric cancer. The use of essential bioinformatics tools like COSMIC and KEGG empowers researchers to identify somatic mutations and comprehend the genetic underpinnings of cancer progression. Furthermore, the application of computational tools such as DynaMUT allows for the prediction of how mutations can impact protein behavior, a critical aspect of structural biology and protein engineering. To complete this holistic journey, the article spotlights SwissDock, a potent platform for drug discovery, enabling the prediction and analysis of interactions between small molecules and target proteins. Notably, the inclusion of TrastuzumabEmtansine, Sunitinib, and Olaparib underscores their significance in the realm of cancer treatment, especially within the context of personalized medicine and structure-based drug design for gastric cancer. These drugs, each with their unique mechanisms and targets, hold promise in advancing the field of oncology and offering tailored solutions for patients. The interdisciplinary nature of structural biology and bioinformatics, as showcased in this article, emerges as a cornerstone in advancing our understanding of complex biological processes and shaping the future of precision medicine in the fight against cancer.

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