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Special Issue: Computational drug designing and molecular docking analyses

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Thyroid Cancer TC-1: an insight from 3D structure prediction to virtual screening for computational drug design

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Abstract

A Thyroid cancer 1 (TC-1) disordered protein overexpressed in thyroid carcinogenesis mainly to vertebrate, and thyroid cancer associated genes do not have a common homology. Its rate of deaths depends upon the type of thyroid cancer 1. The impact of TC-1 in papillary carcinoma showed more expression of thyroid cancer among other tumors. The protein was involved in various biological processes such as wnt/β catenin signaling pathway involved in thyroid cancer. The TC-1 undergoes a detailed sequence analysis that provides the information in conserved part region among primates, birds, rodents, and reptiles. Additionally, different prediction tools and software were utilized for the prediction of thyroid cancer 1 protein. The string database was used for protein- protein analyses that were performed with LSM1 interacting protein and seek the protein interacting residues by computational approach. The comparative docking was performed by utilizing ZINC library compound and generated an efficient result by selecting the compound having least binding affinity for the analysis of computational drug designing.

Introduction

Thyroid Cancer (TC) is the irregular growth of cells in thyroid glands that makes hormones to control the blood pressure, body temperature, heart rate, weight and mostly the malignancy of the endocrine system of head and neck. TC is classified into four different types. The papillary thyroid cancer (PTC), arise from follicular cells, which develop, and store thyroid hormones and 80% thyroid cancer fall in PTC. Follicular thyroid cancer (FTC) arises from the follicular cells of the thyroid. Medullary thyroid cancer (MTC) initiates in the thyroid cells known as C cells that produce the hormone calcitonin and anaplastic thyroid cancer (ATC) is a rare type of thyroid cancer that begins in the follicular cells. Thyroid cancer is known to be the 7th common most cancer among the females, meanwhile the 14th most common cancer in males [1, 2]. According to the world cancer statistics report of 2018, 0.4% death rate has been raised due to TC [3, 4]. There are environmental and genetic risk factors observed such as goiter in any family history, emissive radiation exposure and certain hereditary syndrome. The key cause of TC is still not known [5].

The transcriptional expression level and an immune response regulator (*TC-1* or *TCIM* or *C8orf4*) are involved in the proliferation of TC. There is no homology sequences of *TC-1* located at chromosome 8 (8p11.21) [6]. Thus, several studies reveal that the TC has association with a related Wnt/β-catenin signaling pathway as β-catenin and axin play the curial involvement for TC mutations. The WNT-CTNNB1 pathway enhances the CBY1 activity [7, 8]. The protein is used to intensify the follicular dendritic cell proliferation [9]. Mitogen-activated MAPK2/3 also plays by this protein for signaling the pathway, regulates the transition of the cell cycle from G1 to S phase [10]. The promoter of cell proliferation in cancer as PTC or lung cancer, G1-to-S-phase transition and inhibitor of apoptosis [11].

The TC-1 has 106 amino acids, which activate the proteosomal degradation rapidly. It stimulates the expression by heart shock, certain cell stresses, as well as pro-inflammatory cytokine [12]. Recently, Parkinson's disease is executed by genome-wide association study (GWAS), considering an abnormal regulation of blood vessels in brain [13]. The TC1 is associated with breast cancer, gastric carcinoma and hypertrichosis universalis congenita. The protein function plays a role as constructive regulator in Wnt/β-catenin signaling pathway to develop the process and cause tumor formation through mis-regulation. Chibby (Cby), a crystal structure of haptocorrin in complex with Cbi binds with β-catenin target *TC-1* are known to engage the antagonistic behavior of cancer [14]. TC-1 binds to Cby which leads to regulate many associated cancers. The cellular evidence the protein mainly localized to the nucleoplasm, to the plasma layer as well as cytosol.

The personalized medicine and computational drug designing from the last decade, have numerous possibilities to understand the cancer diseases that play an important role in medical field [15, 16]. Various biological problems have been demonstrated by applying different approaches of bioinformatics collaborating with structural bioinformatics contributing a crucial role for the cancer drug discoveries, and mutational analyses [17, 18]. The work aims to predict, evaluate and validate of the 3D structure of TC-1 by virtual screening and protein-protein interactional studies [19, 20].

Materials and Methods

The TC-1 protein has not contained any isoform, the amino acid sequence of TC-1 was retrieved from Uniport Knowledge Base having accession number Q9NR00. In the recent work, different computational approaches were performed including sequence analyses, 3D structure prediction, virtual screening and molecular docking analyses.

The genome databases ENSEMBL (http://asia.ensembl.org/index.html) [21] and UCSC Genome browsers (https://genome.ucsc.edu/) [22] were used for the analyses TC-1 sequence location on a chromosome. The composition properties of amino acid sequence were analyses by COILS [23], ProtParam, and ProtScale [24]. To analyses disorder tendency of protein sequence is examine by PONDER tool [25] and alignment is generated by Clustal Omega [26], BLAT and PredictProtein [27].

The sequence of TC-1 was retrieved from Uniprot KB (https://www.uniprot.org/) [28] and for the identification of suitable template against the query sequence subjected to BlASTp. For the modelling MODELLER 9.20 [29] was employed to predict 3D structure by spatial restraints fulfilling. The online tools as IntFOLD [30], RaptorX [31], CPHModel [32], EsyPred3D [33], HHpred [34], Phyre2 [35], Robetta [36], SWISS-MODEL [37], I-TASSER [38], SPARKS-X [39], M4t [40], MOD-WEB [41] and 3D-JigSaw [42] were employed for protein structure prediction. For visualization of protein 3D structure, UCSF Chimera 1.13 [43] and Pymol [44] Software were used. The minimization of the predicted

structure was performed by UCSF Chimera 1.13. MolProbity [45] online server was used to evaluate the predicted structure. Various evaluation tools including Rampage [46], ProCheck [47], Anolea [48], Verify 3D [49], and Errat [50] were utilized to determine the protein structure quality.

To determine functional partners of the target protein, STITCH (Search Tool for InTeracting CHemical) [51]and STRING (Search Tool for the Retrieval of Interacting Genes/Protein) [52] databases were employed for TC-1. The crystal structure of C8orf4 (PDB ID: 4m75) was retrieved from PDB. The online server Patch Dock [53] was used for the docking interaction and Fire Dock [54] was employed to refine the analyses. Gramm-X [55] online server was also utilized for the analyses of protein-protein docking studies. The hydrophobic and electrostatic interactions were analyzed through LigPlot [56, 57].

The molecular docking analyses were performed by using Pyrx [58] by optimizing AutoDock. The blind docking analyses were carried out to analyze the interactions between the protein and ligands for the orientation and conformation. FDA library of was extracted from the zinc database [59] and virtually screened against the target protein and these screened molecules are further used for the drug designing [60, 61].

Results and Discussion

The study of structural bioinformatics is the field of exploring knowledge and providing research in an efficient way for the better understanding and development of different research approaches that helps us for the detection of disease along with the treatment procedures and medicines. The TC-1 protein showed over expression in PTC as compared to other types of TC.

Sequence Analyses

The location of the gene position was determined by using ENSEMBLE and UCSC genome browser databases as chromosome 8 having position 8p11.21contain the gene of *TC-1* on the forward stand of open reading frame 4 which contain 1829 base pair nucleotides (**Fig. 1**).

Fig. 1: The presence of gene TC-1 on the position of chromosome number 8 (8p11.21) upon the forward stand that contain 1829 bp.

The multiple sequence alignment (MSA) was performed by Clustal Omega to evaluate the protein similarities among the family in which '*****' show the identical residues, "**:**" describe the similar residues among all three-protein family of TC-1 (**Fig. 2**).

COILS, ProtParam and ProtScale tools were utilized to calculate the physiochemical properties as molecular weight of the protein was on the average isotope masses of amino acid and the average isotope mass of one water molecule. The extinction coefficient will be 10% chance of error as the sequence does not contain tryptophan (W). Theoretical pI depends on the side chain which plays an important role to determine the pH of the protein. The half-life of the protein was observed 30 hours in vitro. The number were negative atoms as well as positive charges residues along with total number of atoms and aliphatic index were calculated (**Fig. 3**).

```
sp|Q9NR00|TCIM_HUMAN     MKAKRSHQAVIMSTSLRVSPSIHGYHFDTASRKKAVGNIFENTDQESLERLFRNSGDKKA  60
sp|Q9D915|TCIM_MOUSE     MKAKPSHQATSMSSSLRVSPSIHGYHFDTAARKKAVGNIFENIDQESLQRLFRNSGDKKA  60
sp|Q5E969|TCIM_BOVIN     MKAKPSHPAFSMSTSLRVSPSIHGYHFDTASRKKAVGNIFENIDQEALQRLFRNSGDKKA  60
                         **** ** *  **:***************:********** ***:*:**********

sp|Q9NR00|TCIM_HUMAN     EERAKIIFAIDQDVEEKTRALMALKKRTKDKLFQFLKLRKYSIKVH        106
sp|Q9D915|TCIM_MOUSE     EERAKIIFAIDQDLEEKTRALMALKKRTKDKLLQFLKLRKYSIKVH        106
sp|Q5E969|TCIM_BOVIN     EERAKIIFAIDQDLEEKTRALMALKKRTKDKLFQFLKLRKYSIKVH        106
                         ***********:****************:***********
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Fig. 2: Alignment retrieved from the Clustal Omega of the related protein of mouse and bovine with a human which shows residues with *(identical) and :(somewhat similar).

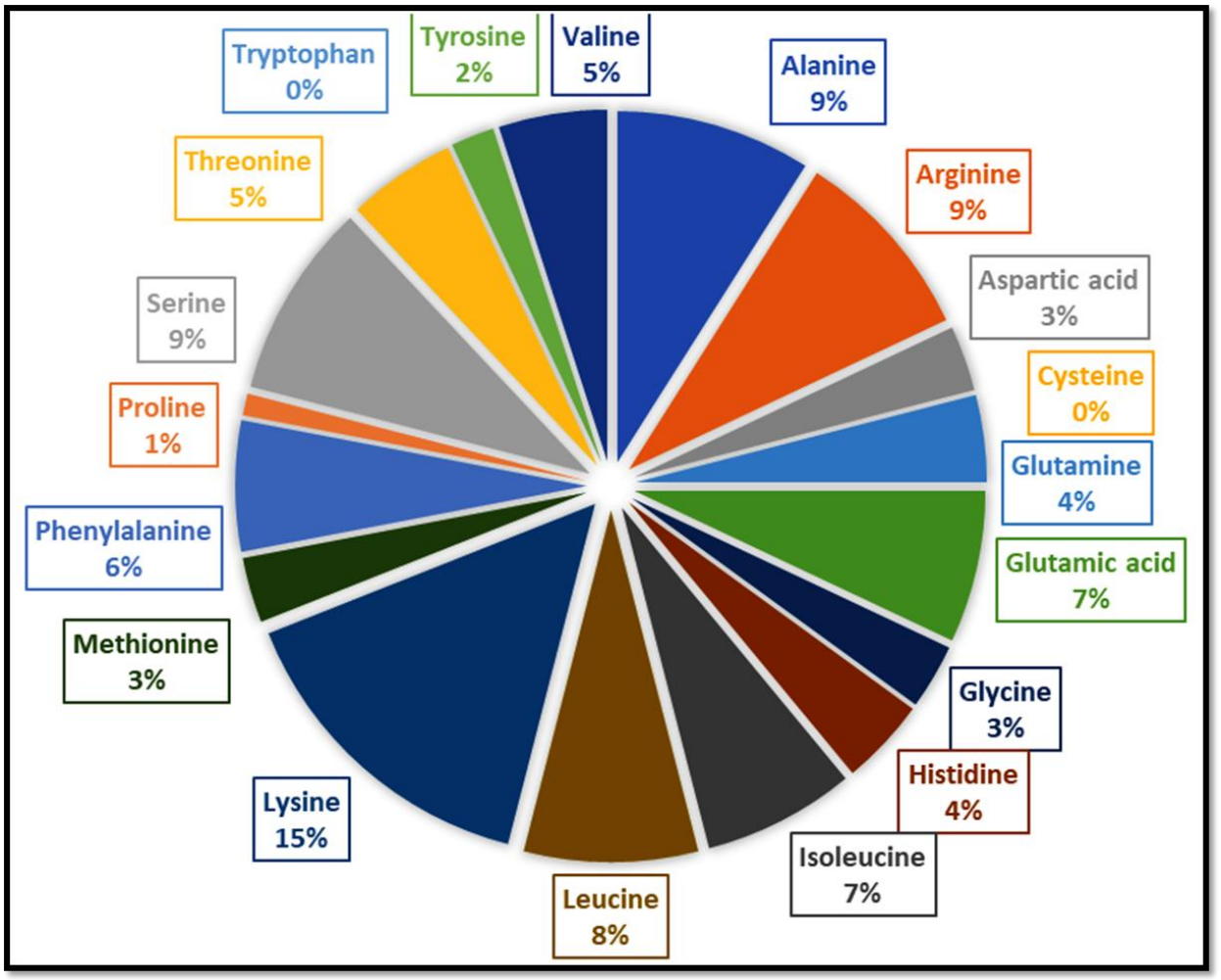

Fig. 3: Pie chart representation of composition amino acid (a.a) of TC-1 and calculated percentage values.

The neural network-based protein disorder was predicted in the region of TC-1 cancer reveal that 65 residues were involved in disorder region and approximately 61 percent of the total protein. The PONDR tool was trained to detect the disorder sequence to determine the sequence mutations. TC-1 has two chains and one have a long stretch of 52 residues (38-89). The graph showed that the order and disorder composition as middle single line was threshold and above the line lies in the disorder region sequence. Therefore, TC-1 was predicted as a natively disordered protein (**Fig. 4**).

Structure Prediction

3D structure of TC-1 (TCIM; C8orf4) was not reported by NMR and X-ray crystallography techniques till now. To predict the 3D structure, comparative and threading approaches were used. The sequence was submitted to BLASTp against PDB to retrieve suitable templates. The top-ranked five templates having maximum identity, E-value, query coverage and total scores were observed for homology modeling. All the scrutinized templates were utilized to generate 3D structure of TC-1 (TCIM; C8orf4). The total query coverage along with similarity for the used template against TC-1 showed >70% from end to end for homology modeling analyses.

Several models were generated by utilizing various tools (Robetta, Phy2, M4t, HHpred, SWISS MODEL, SPARKS-X, Raptor-X, PSIPRED, IntFOLD, Mod Web, 3D-jigsaw, I-TASSER, and MODELLER 2.0) as in silico approaches (threading and comparative modeling) to predict the structures.

All these generated models were evaluated based on quality factor, favored region, allowed region and outliers. The graphs were generated comparatively for all the predicted models from the homology and threading approaches and the reliable structure was selected from the generated graphs (**Fig. 5**).

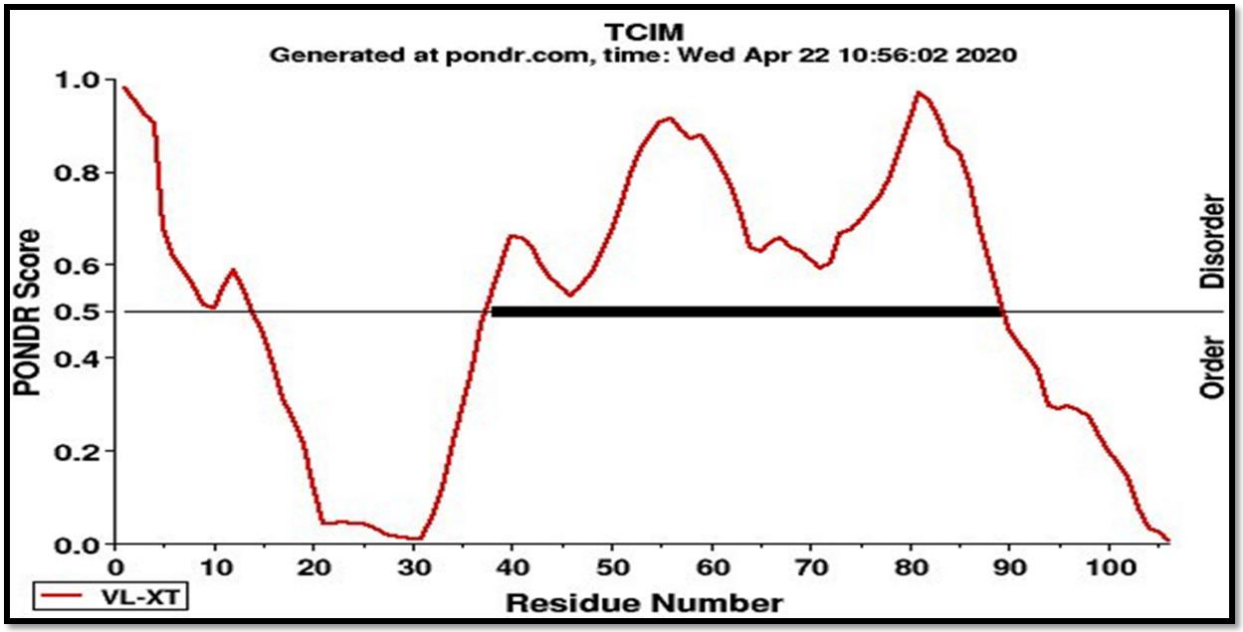

Fig. 4: Peak graph shows the disorder of residues score TC-1 protein, X-axis values are the number of residues in the graphs and the Y-axis elaborate about the order and disorder scores.

The overall quality factor showed of TC-1 was 93.62% accurate evaluated from the ERRAT. Ramachandran plot were utilized for the evaluation of predicted model which reveals the φ and ψ distributed along with the information of residues of favored region lie 98%, allowed region residues consist of 99% of the total sequence and only one residue exist in outlier region Val 105. The minimization of the selected structure was applied for the improvement of stereochemistry and considered the model for the most optimal purpose. The most optimal structure was minimized at UCSF Chimera 1.13 on 1000 steepest and conjugates gradients runs after the critical examination at evaluation parameters (**Fig. 6**).

Protein-Protein Interactions

The TC-1 expressed in lungs, thyroid, and nuclear expression in several tissues, mostly in placenta. The crystal structure of LSM1 complex was the interacting partner of TC-1, was used for the interaction of protein- protein docking studies. The protein-protein docking analyses were performed and determined by using GrammX online server. The interacting residues of the complex were analyzed through UCSF Chimera 1.13 (**Fig. 7**). The interacting residues of receptor protein and ligand protein were analyzed (**Table 1**) [62].

Molecular docking analyses

The molecular docking experiments revealed different binding energies and complexes were generated. The least binding energy complex was determined by analyzing the least binding energy and was selected for further analyses. The structure accuracy was determined though docking which was employed by PyRx. The Zinc library compound ZINC00010 showed least binding energy of -8.5 Kcal/mol (**Table 2**). The 2D structure (**Fig. 8**) of the selected compound was minimized through ChemDrawUltra 8.0 [63]. The 3D structure analyses of molecular docking were analyzed through Chimera 1.13 (**Fig. 9**).

The specificity of functional proteins related to its structure is involved in cellular processes as they are molecule of life. Bioinformatics field in which various disciplines including computing, bioinformatics, mathematics, artificial intelligence, chemistry and statistical approaches were covered to facilitate discovery of new biological ideas [64]. Structural bioinformatics field has undergone many improvements over the last 10 years. Computational recourses increase in biological data and methodology develop the size and resolution of study as well as created complex question to research

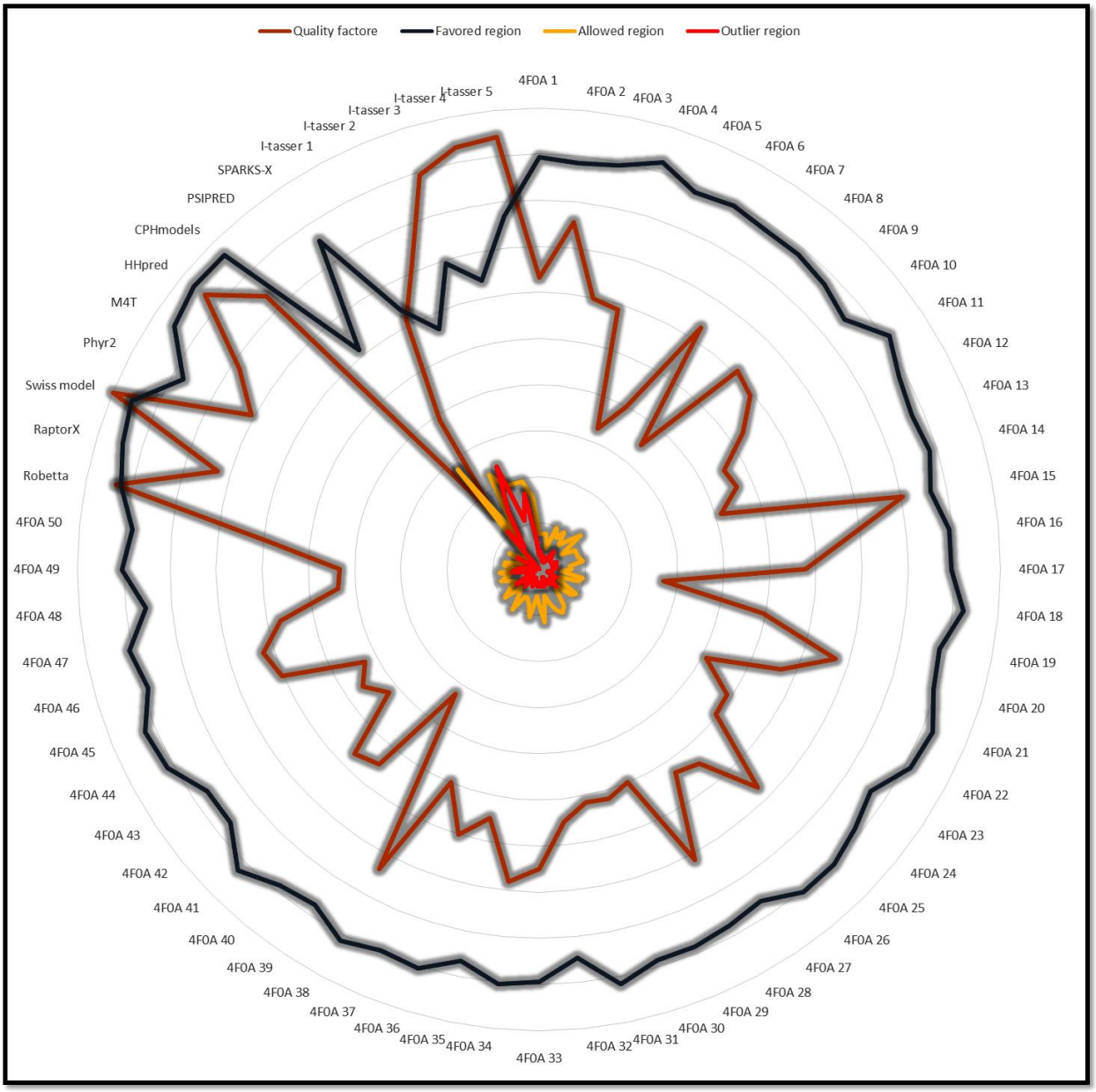

Fig. 5: Graph of Quality Factor, Favored Region, Allowed Region and Outliers region of the TC-1 Protein structure prediction analysis extracted from the different modeling tools and software

[65-67]. The study of protein and information related to protein open many questions that are related to health of an organism. The approaches of computational analyses lower the time phases and very useful to the researcher in the field of research[68-70]. By using in silico methods and computational approaches the protein structure of TC-1 was predicted.

Conclusion

Computational bioinformatics analysis on TC-1 protein that causes thyroid cancer in the human forecast the 3D structure of the protein sequence. The docking approaches were implemented for protein-protein interaction as well as to seek out the ligand-based docking analysis with the thyroid cancer 1

protein. These docking analyses will be utilized for computational drug designing and development.

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Conflicts of Interest

The authors declare no conflicts of interest.

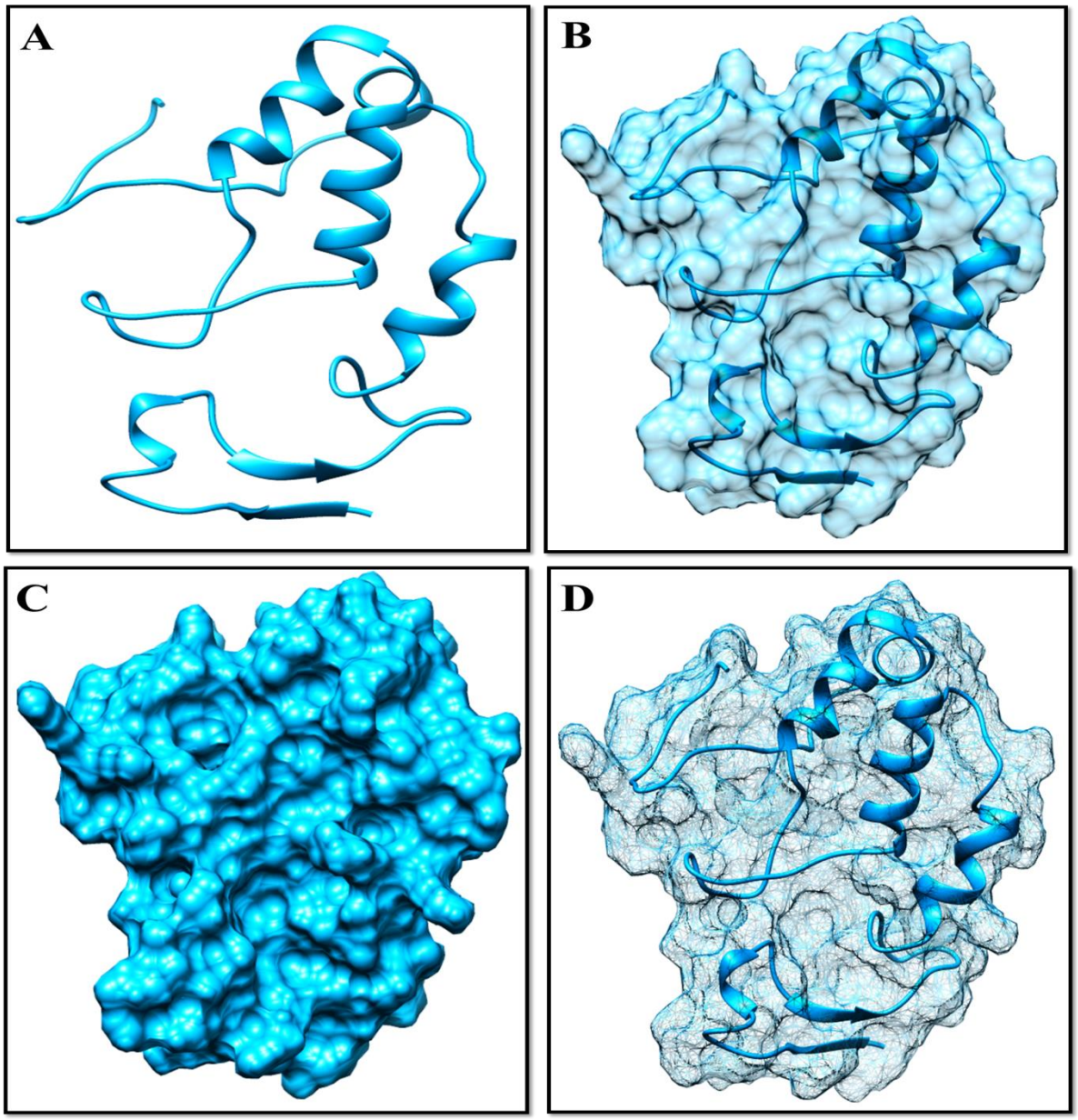

Fig. 6: 3D-Structure image predicted from the modeling tool (Robetta) declared the optimal structure of TC-1 protein.

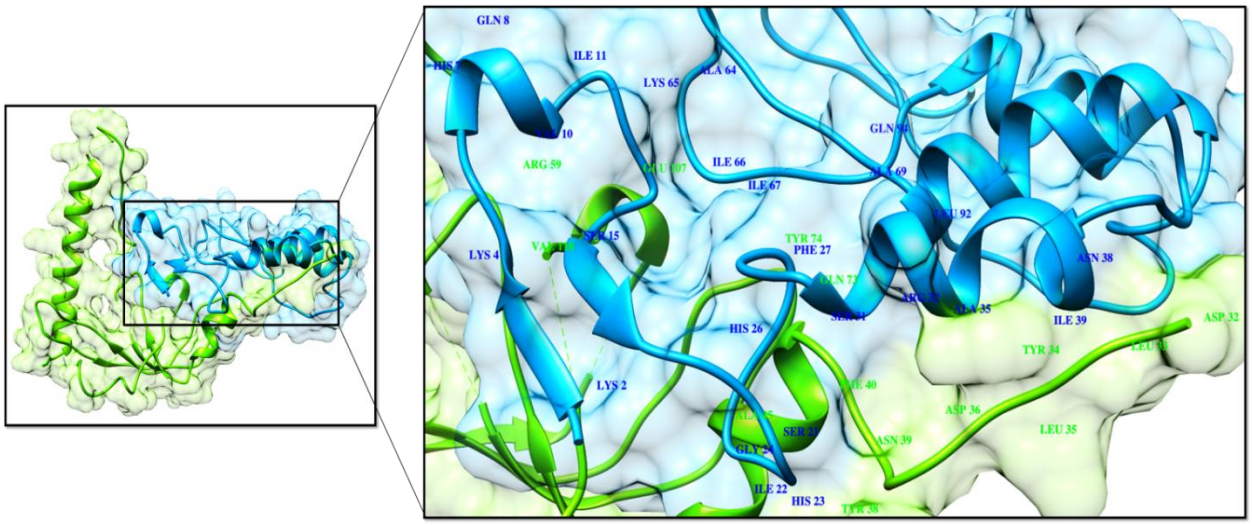

Fig. 7: Protein-protein docking structures.

Table1: Residues of protein-protein docking as receptor protein and ligand protein.

Target Protein	Target Protein residues	Interacting protein	Interacting Protein residues
Thyroid Cancer-1	LYS 4, GLN 8, VAL 10, SER 15, SER 21, GLY 24, ARG 32, ALA 35, ASN 38, ILE 39, GLN 94	LSM1	ASP 32, LEU 33, TYR 34, LEU 35, ASP 36, GLN 37, TRY 38, ASN 39, PHE 40, THR 41, THR 42, THR 43, ALA 44, ALA 45, ILE 46, VAL 47, SER 48, SER 49, VAL, ASP 51, ARG 52, LYS 53, ILE 54, PHE 55, VAL 56, LEU 57, LEU 58, ARG 59, ASP 60, GLY 61, ARG 62, LEU 64, PHE 65, GLY 66, VAL 67, LEU 68, ARG 69, THR 70, PHE 71, ASP 72, GLN 73, TYR74, ALA 75, ASN 76, LEU 77, LEU 78, LEU 79, GLN 80, ASP 81, CYS 82, VAL 83, GLU 84, ARG 85, ILE 86, TYR 87, PHE 88, SER 89, GLU 90, GLU 91, ASN 92, LYS 93, TYR 94, ALA 95, GLU 96, GLU 97, ASP 98, ARG 99, GLY 100, ILE 101, PHE 102, ILE 104, ARG 105, GLY 106, GLU 107, ASN 108, VAL 109, VAL 110, LEU 112, GLY 113, GLU 114, VAL 115, ASP 116, ILE 117, ASP 118, LYS 119, GLU 120, ASP 121, GLN 122, PRO 123, LEU 124, GLU 128, ARG 129, ILE 130, PRO 131, PHE 132, LYS 133, GLU 134, ALA 135, TRP 136, LEU 137, THR 138, LYS 139, GLN 140, LYS 141, ASN 142, ASP 143, GLU 144, LYS 145, ARG 146, PHE 147, LYS 148, GLU 149, GLU 150, THR 151, HIS 152, LYS 153, GLY 154, LYS 155, LYS 156, ALA 158, ARG 159, HIS 160, ILE 162, VAL 163, TYR 164, ASP 165, PHE 166, HIS 167, LYS 168, SER 169, ASP 170

Table 2: Top four least binding energy compounds from the molecular docking experiment.

Name of compound	Binding affinity kcal/mol	RMSD/ upper binding	RMSD/ lower binding
ZINC00010	-8.5	3.37	11.229
ZINC00130	-8.2	0	0
ZINC00131	-8.2	0	0
ZINC00093	-7.9	0	0

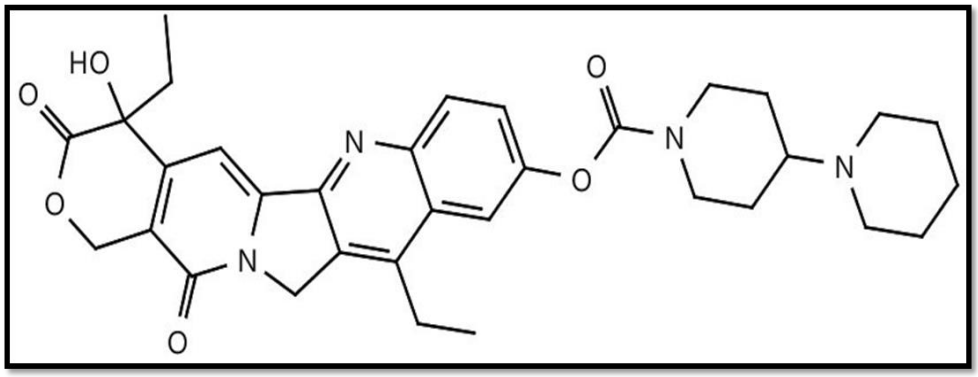

Figure 8: 2D-Structure of least binding affinity structure compound.

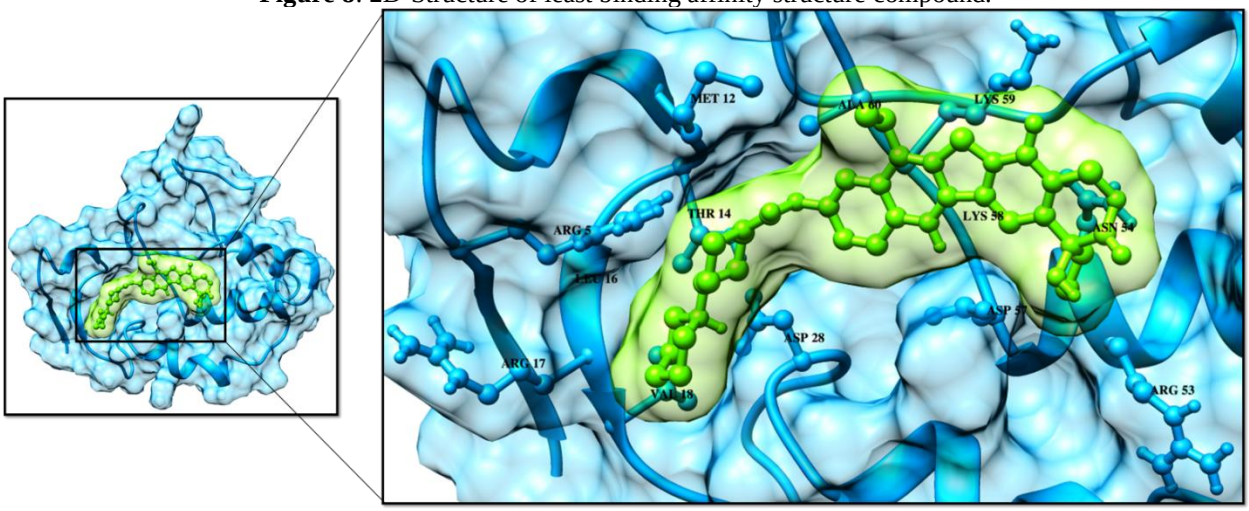

Fig. 9: Molecular Docking analyses of least binding energy compound through virtual screening.

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