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Drug Repurposing of Anticancer Agents JP-8g and REDX05358 Against the Target Protein Plectin 1a in Epidemolysis Bullosa Simplex with Muscular Dystrophy (EBS-MD)

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Abstract

Epidermolysis Bullosa Simplex with Muscle Dystrophy is a genetic disease affecting the skin and muscles which can be seen at birth or start at adulthood due to the mutation in the protein Plectin 1a (PLEC gene) causing skin blisters and muscle weakness. This protein is seen in sarcolemma, Z disks in skeletal muscles, hemidesmosomes in skin and cardiac muscles giving stability to cytoskeleton, playing a crucial role in neuromuscular transmission but when get mutated it leads to lack of cytoskeleton support in connecting the intermediate filaments to microtubules, myosin and actin filaments. This research aims at treating this disease with two anticancer agents against the mutated plectin1a. Different bioinformatics tools are used to get the effectiveness of the two anticancer agents against the therapeutic target protein. Molecular docking between the drugs and target in PyRx screening software and further visualization of those interactions in BIOVIA Discovery Studio are done. SwissADME tool evaluated the pharmacological properties of the drugs. Three ligand molecules JP-8g, REDX05358 and CAY10736 were selected for molecular docking with high negative binding affinity (least binding affinity) and pharmacological properties of two were studied. Anticancer agents JP-8g and REDX05358 are finally selected for drug repurposing against the mutated plectin 1a in EBS-MD as they give good molecular docking score and good ADME properties.

Keywords: Epidermolysis Bullosa Simplex with Muscular Dystrophy (EBS-MD), plectin 1a acting binding domain, ligands, JP-8g, REDX05358, PyRx, molecular docking, BIOVIA, ADME

INTRODUCTION

The autosomal recessive disorder Epidermolysis Bullosa Simplex with Muscle Dystrophy (EBS-MD) is a severe genetic disorder of epithelia causing skin blisters (around neck, nails also in mouth) which may lead to hemorrhage and causes muscle weakness starting at the early infant stages or after some years in adults. This severe case of the body is caused by the mutations in the PLEC gene located on 8q24 chromosome encoding for protein Plectin-1a (HGNC: 9069 NCBI Gene: 5339 Ensembl: ENSG00000178209 OMIM®: 601282) which is a multifunctional cytolinker (500KDa) seen in higher amount in squamous epithelial and muscle tissues. The protein plays a crucial role in cytoskeleton stability, cell and tissue integrity (EBS-MD; OMIM# 226670) Plectin belongs to the plakin family of proteins and reacts with keratin, beta 4 integrins and is a component of hemidesmosomes. Myofibrillar intermediate apparatus and aberrant binding of hemidesmosomes to intermediate

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filaments present in the cytoskeleton is a consequence [1–3]. It not only binds to all types of IFs in the cytoskeleton (actin filaments and microtubules) but also to transmembrane receptors, other proteins of the skeleton, components of the nuclear envelope, and several kinases. As the protein is mutated in EBS-MD, it undergoes great mechanical stress leading to erosions in skin and oral mucosae and delayed walking. Not only EBS-MD, it also causes EBS with pyloric atresia, and EBS-Ogna [1]. Small white bumps on the skin, difficulty swallowing (dysphagia), thickened calluses on the palms of your hands and soles of your feet, blisters on knees, elbows, hand, feet) or inside your body are the effects of this disorder. There is no cure for EBS-MD. Preventing skin blisters, and management of pain can be done as a part of protecting your body. Hemidesmosomes of the skin have plectin with keratinocytes (in the epidermis) and the stability to these keratinocytes are also provided by plectin protein. Plectin is related to actin and keratin [4–7].

Most mutations causing EBS-MD to have concentrated on exons 32 and 33, but every part of the gene will also get this mutation. Intraepidermal blisters and dermal mononuclear inflammatory infiltration are shown in skin biopsy. Muscle biopsy demonstrated characteristic dystrophic changes which include muscle around the shoulders, eyes and chest. There is a case report of EBS-MD having a homozygous in-frame deletion mutation in the PLEC gene which contains 7 mutations extremely affecting plectin protein. A desmin protein aggregate myopathy phenotype is seen when the PLEC gene is mutated because plectin is the key cytolinker protein that regulates the structural and functional organization of desmin filaments. A key pathogenetic event happens which is the formation of desmin protein aggregates and a secondary mitochondrial pathology occurs as a result of the defective anchorage of desmin filaments [5].

Drug repurposing is a lead in the field of drug discovery as it identifies compounds with high therapeutic value and works by phenotypic selection [5–11]. Drug repurposing has helped the cells with this chemotherapeutics when they become mutated [3, 12–16]. Approaches for drug recycling include computational approaches, biological experimental approaches, and mixed approaches. To know how the drug repurpose affects the target, the pathway of the target protein should be evaluated. The target protein of this research paper, which is mutated plectin 1a, unstabilizes neuromuscular junctions by weakening the connection of the IF cytoskeleton to the hemidesmosomes. The drug repurposing in EBS-MD aims at reversing the unstable cytoskeleton in the epithelial tissue and in muscles which gives good anchorage to IF filaments to the hemidesmosomes [17–20]. Here Target-based method of drug repurposing is used where the 3-D structure of protein are retrieved, canonical SMILES are used for pharmacological studies and molecular docking of the molecules are done [21].

This research project presents anticancer agents that can be pharmacologically treated against the mutated protein plectin 1a actin binding domain which is the diagnostic biomarker and potential target in the disorder epidermolysis bullosa simplex-muscular dystrophy [1].

METHODOLOGY

A genetic disorder characterized by blistering and later-onset muscle mutations in EBS-MD is caused by the PLEC gene located on 8q24 encoding plectin 1a isoform of protein plectin. Virtual screening and molecular docking studies are carried out with anticancer agents against the mutating target protein to stabilize the cytoskeleton and to regain cell and tissue integrity. Binding of anticancer compounds to the active sites of plectin 1a inhibits the mutation as well as its deficiency in muscles and epithelial tissues. It functions as a potent oncoprotein because of its cancer specific mislocalization to the cell.

Protein Retrieval

The 3-D crystal structure of the protein of interest plectin 1a actin-binding domain (PDB ID:4q58) (UniProtKB/Swiss-Prot: Q15149) is retrieved from RCSB PDB Database (https://doi.org/10.2210/pdb4Q58/pdb) based on its mutation properties given by the Human Gene Database, GeneCards (https://www.genecards.org/). The determination of this protein is done by X-

Ray diffraction method and the resolution obtained for protein is 4.00 Å. The protein is further purified in BIOVIA Discovery Studio for molecular docking in PyRx virtualizing software tool.

Ligand's Retrieval

The 2-D SDF (Structural Data File) structure of 50 anticancer agents are retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) to treat against the tumor biomarker plectin 1a. These are anticancer agents having toxic effects on several cancer cell lines with good IC_{50} values. Different anticancer agents show different chemical and physical properties in PubChem database which includes the pharmacological properties. These ligands are predicted to have pharmacological activity against the mutated drug plectin 1a present in the skin and muscles.

Purification of Protein

The retrieved 3-D structure of protein plectin 1a is opened through BIOVIA Discovery Studio for purification. This tool enables you to view the 3-D structure, residue, atoms and different type of forces in a protein. The protein plectin contains A, B, C and D chains, protein groups and other heteroatoms. All the heteroatoms are removed as they will interact with the ligand molecule while docking. Removing of B, C and D chains and other heteroatoms is followed by addition of polar hydrogen atoms into the protein structure. Macromolecules are present in charged form with no atom missing in human body. So, it is necessary to add charges and missing hydrogen atoms to the protein for the AutoDock Vina algorithm (in PyRx software) to run calculations with. Thus, the purified 4q58 protein is obtained as in Figure 1 which is saved in the pdbqt format in BIOVIA visualizing software tool [22–25].

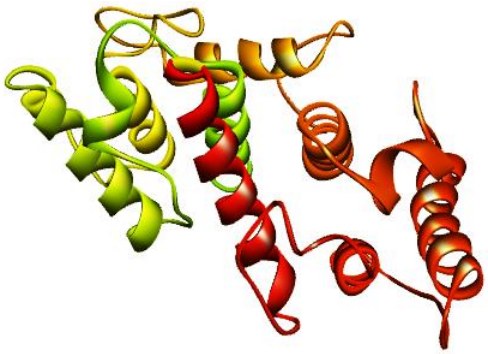


Figure 1. Purified protein plectin 1a (PDB ID: 4q58).

Molecular Docking Analysis by PyRx Virtual Screening Software

The PyRx virtual screening software enables screening of 50 anticancer drugs (ligands) against the potential drug target. PyRx recognizes protein plectin 1a as a macromolecule to interact with its ligands. The tool uses AutoDock Vina algorithm to improve the speed and accuracy of docking. The first step involves importing the saved purified 4q58 protein which is in pdbqt format from BIOVIA to PyRx and then converting the protein into a macromecule. Then by selecting "AutoDock", "Open Label" feature of PyRx is clicked to import all the downloaded anticancer agents or the ligands (from PubChem). 50 ligands are imported, one at a time followed by energy minimization of all the ligands and converting them all to AutoDock PDBQT (this is for adding torsion angles (t) and Kollman charges (q) to maintain the flexibility of the ligand to bind the protein and electrostatic interaction between protein and ligands, respectively, while the ligands are rotating) prior to screening. Then Vina Wizard is selected for generating grid boxes for both protein and ligands. This grid box gave the grid dimensions for X-coordinate (58.9375Å), Y-coordinate (49.5779 Å) and Z-coordinate (44.0832 Å) to set the boundary for docking. Finally molecular docking is initiated, it reads the input, sets the scoring functions [4, 5]. and search for the binding site in the protein macromolecule to get the best binding confirmations with the ligand molecules.

Once it's completed the excel sheet of the 450 confirmations of 50 ligands (anticancer agents) with its binding energy and Root Mean Square Deviation (RMSD) value is saved in CSV file [26–29].

Filtering compounds having zero RMSD value and high negative binding affinity gives 4 ligand molecules.

The three ligand molecules obtained are JP-8g which is anticancer agent 236 (PubChem CID: 71627205), REDX05358 which is anticancer agent 124 (PubChem CID: 118948409) and CAY10736 which is anticancer agent 225 (PubChem CID 145988076) are shown in Table 1. They are obtained with high negative binding affinity (least binding affinity) and zero RMSD value. The interaction between the ligands and the purified protein is visualized in BIOVIA Discovery Studio.

Table 1. Ligands with PubChem CID and Molecular Formula.

Ligands	PubChem CID	Molecular Formula
JP-8g	71627205	$C_{27}H_{17}F_2N_3O_6$
REDX05358	118948409	$C_{26}H_{21}ClN_4O_3$
CAY10736	145988076	$C_{41}H_{59}N_3O_3S$

Visualization in BIOVIA Discovery Studio

BIOVIA Discovery Studio tool enables the visualization of 2-D and 3-D models of selected three ligands interaction with the receptor molecule. The visualization defines the hydrogen bonds, charges and the binding of the ligand molecules to the active sites in the amino acid residues of the protein. This interaction predicts the 4 ligand molecules can be a promising drug for the target molecule.

In Silico Pharmacological Studies

Determining the pharmacological properties of the four anticancer agents in SwissADME tool present with two anticancer agents. At first, the canonical smiles of 4 ligands are pasted in SwissADME tool (http://www.swissadme.ch/) to obtain the pharmacokinetics of the drugs. JP-8g (PubChem CID 71627205) and REDX-05358 (PubChem CID 118948409) are predicted to be the best therapeutics for the plectin 1a protein based on molecular weight, hydrogen acceptor, hydrogen donor properties which obey the Lipinski rule, whether the ligand is a substrate for glycoprotein, gastrointestinal absorption and solubility properties. Selection was also based on the PAINS and Brenk alerts. The fraction of sp3-hybridized carbon atoms is also checked to get a compound's saturation level.

RESULT

Protein structure Analysis

Ramachandran Plot

PDBsum database (https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/) is used to generate the Ramachandran plot as well as the secondary structure of the purified protein 4q58. Ramachandran plot of protein plectin 1a actin binding domain displays the phi and psi torsion angles of the amino acid residues present in the purified protein and other stereochemical quality of the protein as well (Figure 2). To describe the backbone of plectin 1a the Ramachandran plot is obtained via PROCHECK which checks the quality of structure given by X Ray diffraction giving different confirmation of amino acids present in protein. 183 amino acid residues give the most favored regions which ensure the protein structure quality, and the blank regions are sterically disallowed to all amino acid residues except glycine which has larger allowed area in the plot. Glycine adopts psi and phi angles in all the quadrants of the plot. There are 10 glycine residues and 6 proline residues, 207 non-glycine and non-proline residues and two end residues which make up the total 225 total amino acids present in the protein 4q58. The main allowed regions come under the beta plated sheets and alpha helical confirmations. The red-colored regions in the second and third quadrant have more allowed regions for confirmation. The blue-colored regions give the most favorable conditions for the torsion angles which are present more in the beta sheet and alpha helix of the secondary structure of the protein. There are 183 favored regions (88.4% of the residues are in the favored region). The score of pi-psi distribution is –0.06 and chi1-chi2 distribution is –0.12. No unfavored regions are seen.

Score –0.16 is only for the dihedral angle chi1. Distribution score of chi 3 and chi 4 angles in the plot is 0.59 and for omega angles it is –0.30. Main chain covalent bond length score is 0.68 and main chain bond angles are 0.55.

The confirmations in light yellow color show no confirmations due to the stearic hindrance (disallowed regions). Since our protein has a good resolution of 4.00 Å, the quality score of the plot is good. The G factor score in the plot –0.07 says the stereochemical property of the protein is normal.

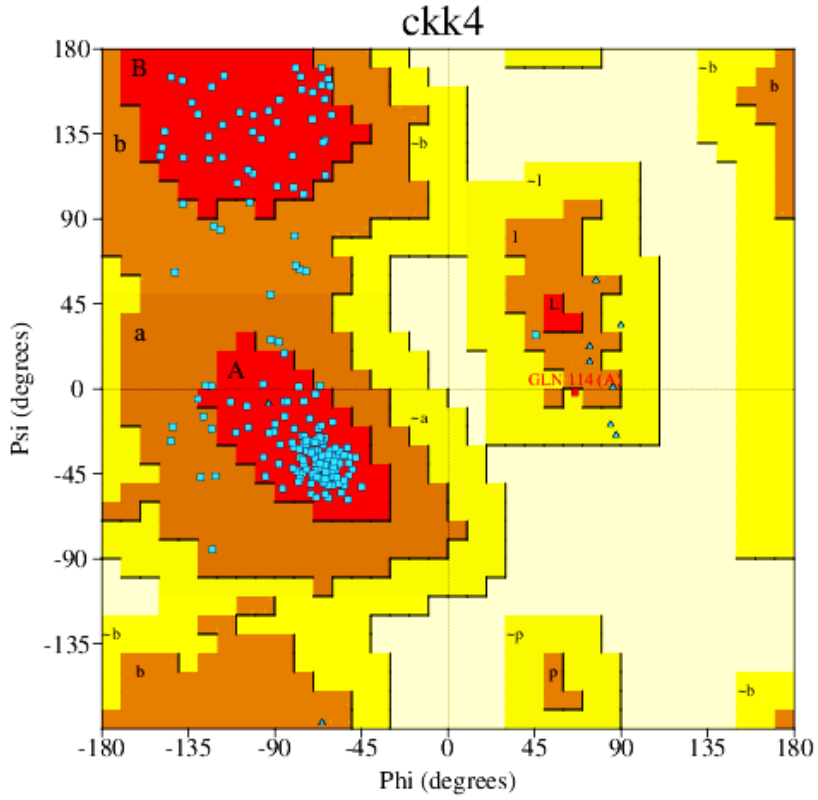


Figure 2. Ramachandran Plot of purified protein 4q58 (PDB id: ckk4) using PDBsum.

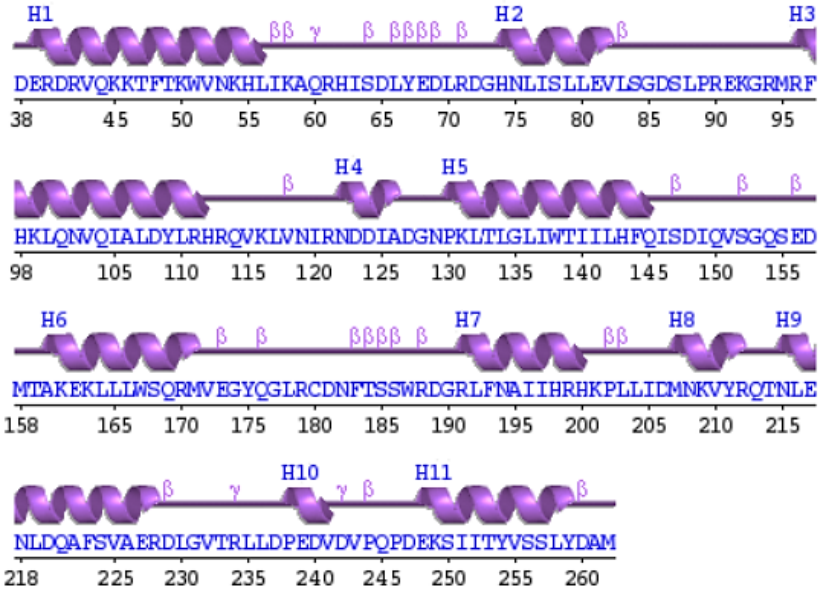


Figure 3. Secondary structure of purified protein 4q58 using PDBsum.

The secondary structure of protein is obtained through PROCHECK (from PDBsum). The secondary structure in purified protein 4q58 has 11 helices. For the stability and the folding of the protein there are 19 helix–helix interactions shown in the structure. 25 beta turns and 4 gamma turns are present in the secondary structure of proteins as given in Figure 3.

Molecular Docking Analysis by PyRx Virtual Screening Software

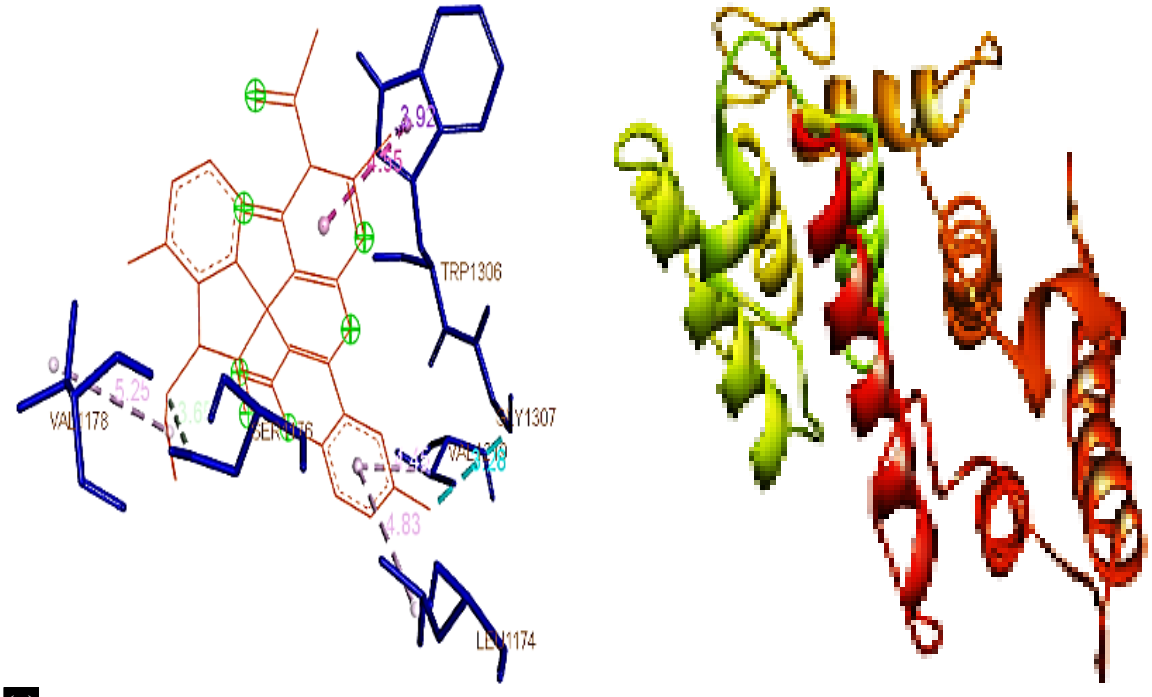
The molecular docking in PyRx virtual screening software gives 3 ligand molecules JP-8g, REDX05358, CAY 10736. Out of these anticancer agent JP-8g and anticancer agent REDX05358 having high negative binding affinity (least binding affinity) –9.5, 9.9, respectively, are selected. These two give zero Root Mean Square Deviation (RMSD) value. Binding affinity of each ligand is shown in Table 2.

Table 2. Binding affinity of the ligands with protein 4q58.

Ligands	Binding Affinity
REDX05358	–9.9
JP-8g	–9.5
CAY 10736	–9.2

Visualization in BIOVIA

The 3 therapeutic drugs JP-8g, REDX05358, CAY 10736 are docked and two drugs having high negative binding affinity (least binding affinity) are selected for visualization in BIOVIA Discovery Studio where they are bind to the active site of the amino acid residues of the purified protein. Here 3-D structure (Figure 4) and 2-D structure (Figure 5) of the interaction of anticancer agents with the receptor molecule is obtained showing amino acid residues of the protein and bond distance between the molecules. The docking results show anticancer drug JP-8g binds with the target protein 4q58 in its active sites of amino acids leucine (1174), serine 1176, valine 1178, valine 1219, glycine 1307, tryptophan 1306. The interactive forces between protein and ligands are given by light green dotted lines representing 1 carbon hydrogen bond from serine residue, 1 violet dotted line representing 1 pi-sigma interaction, 3 light 3 light purple dotted lines indicating 3 pi-alkyl interactions and dark purple dotted line indicates 1 pi–pi interactions. It gives bond distance from each amino acid residues in the protein to the ligand molecule. The bond distances are also shown and the highest bond distance from the protein to the ligand molecules is 5.25 Å.



(a)

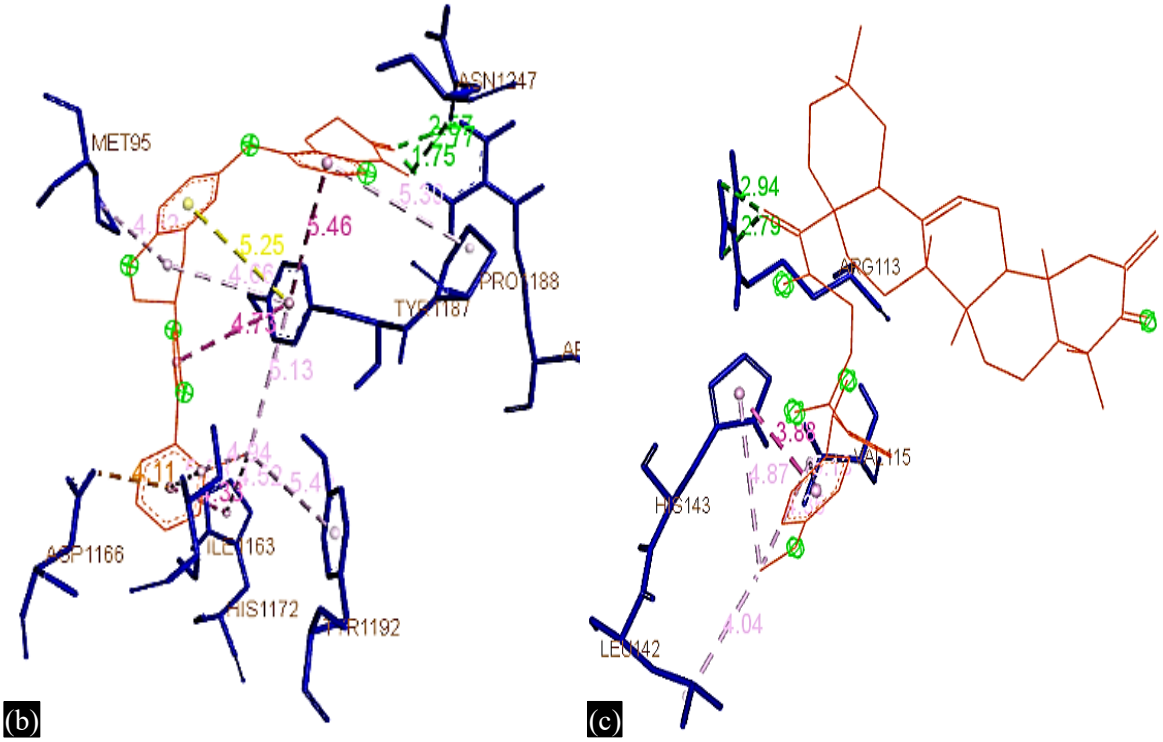
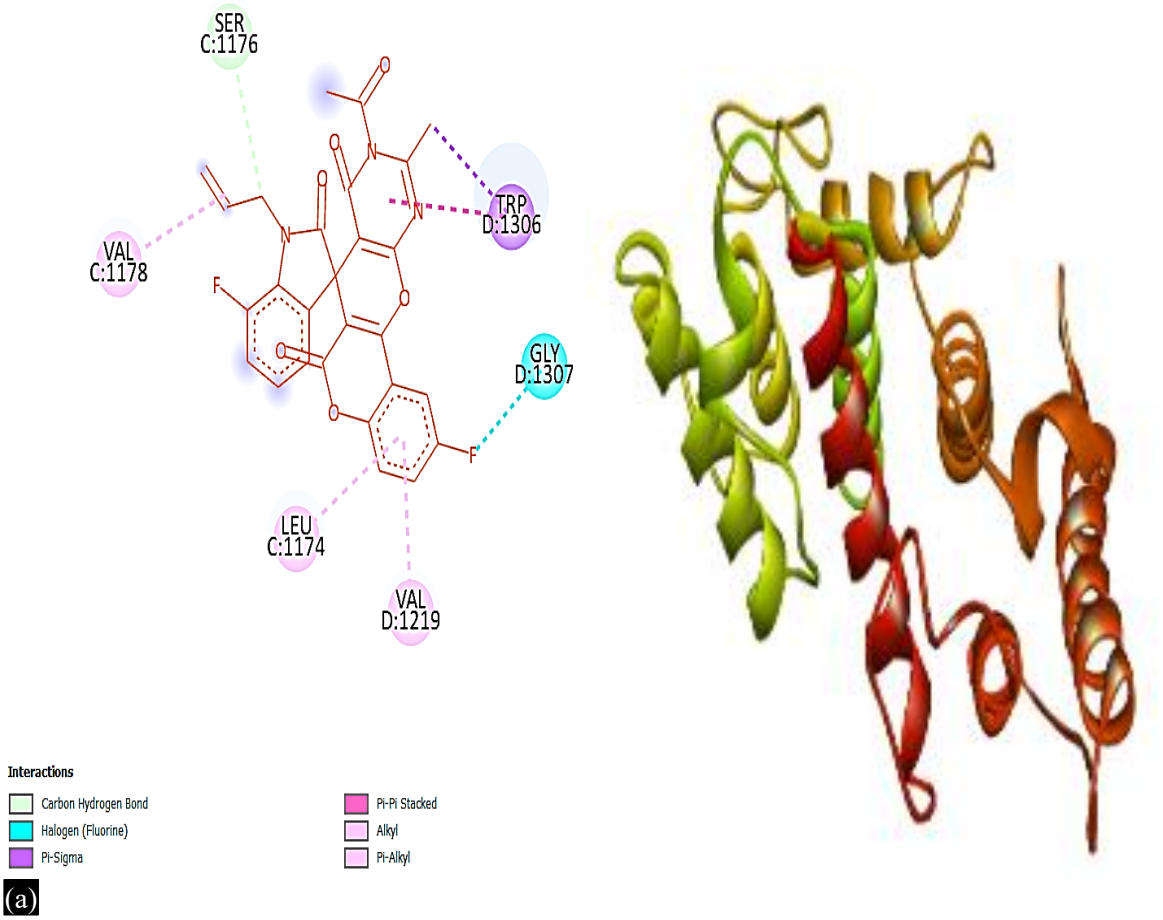


Figure 4. 3-D Molecular docking interaction between (a) anticancer agent JP-8g (CID:71627205), (b) anticancer agent REDX05358 (CID: 118948409), (c) anticancer agent CAY 10736.
(CID: 145988076) with the purified protein 4q58.



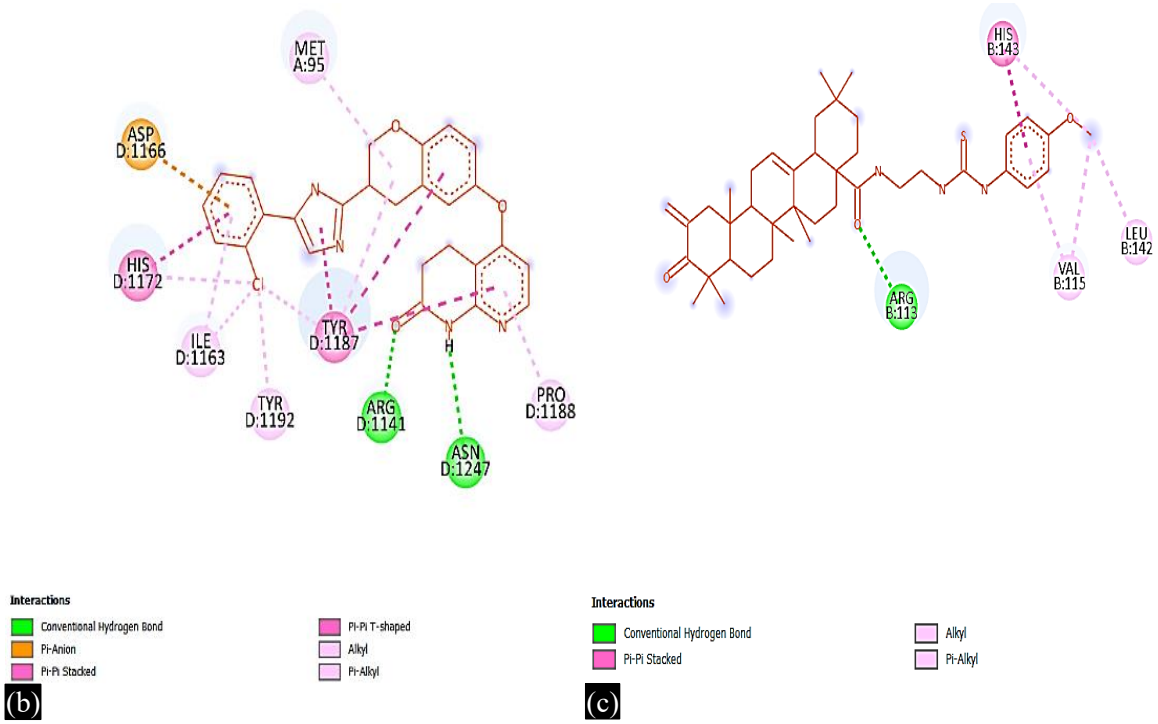


Figure 5. 2-D molecular docking interaction between (a) anticancer agent JP-8g (CID:71627205), (b) anticancer agent REDX05358 (CID: 118948409), and (c) anticancer agent CAY 10736 (CID: 145988076) with purified protein 4q58.

Molecular docking between protein and ligand REDX05358 shows the active sites methionine 95, aspartine 1166, histidine 1171, arginine 1141, tyrosine 1192, isoleucine 1163, asparagine 1247, proline 1188, tyrosine 1187. There are 2 conventional hydrogen interactions between protein and ligand, 1 pi–anion bond between the amino acid and the ligand, pi–alkyl bond and pi–pi bonds and alkyl bonds in its 2-D structure. The highest bond distance between the protein and ligand molecule here is 5.46 Å.

Molecular Docking between the protein and the ligand CAY 10736 gives the active site histidine 143, valine 115, leucine 142, arginine 113. The interactive forces between protein and ligand in the 2-D structure are 1 conventional hydrogen bond, 1 pi–pi stacked interaction and three alkyl interactions and the highest bond distance between the protein and the Cay 10736 ligand molecule have is 4.87 Å.

SwissADME Analysis

Insilico pharmacological studies were done in two anticancer agents. After performing ADME analysis anticancer drug REDX05358 (472.92 g/mol) is found to have some pharmacokinetics properties as the molecular weight of the compound is less than 500g/mol (Table 3), it is found that this ligand is not a substrate for glycoprotein, so the absorption is predicted to be active for this drug (Tables 4 and 5). REDX05358 agrees on Lipinski (molecular weight ≤ 500 g/mol, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5, Molar refractivity should be between 30–140, LogP ≤ 5) value while anticancer drug JP-8g shows 1 violation since its molecular weight is more than 500 g/mol (Table 4). Both satisfy the solubility properties, gastrointestinal absorption property. Hydrogen bond acceptors for both Jp-8g and REDX05358 are 9 and 5 and hydrogen bond donors are 0 and 2, respectively. The pharmacokinetics properties under the Rule-of-five which is the Lipinski rule for the two ligand molecules are given in Table 4. Both the drugs agree on the bioavailability score which is 0.55 but ligand CAY10736 has a bioavailability score which is less than 0.55 (Table 6). Fraction Csp3 which talks about the carbon atoms in the ligand molecules which are sp3 bonded and should be at least 0.25. Lipophilicity helps to know the membrane penetration as well as the transport of the drugs in the body. If the Topological Polar Surface Area is less than 140 Å, the drug is considered to have good absorption.

PAINS and Brenk alerts identifies any frequent hitters and if any toxic chemical constituent are present in the drug, respectively. The rotatable bonds in ligand JP-8g and REDX05358 are 3 and 4, respectively. The predicted toxicity class of these 3 anticancer agents is obtained through Pro Tox 3.0 web server. For REDX05358 the predicted toxicity falls into class 4. Both JP-8g and CAY10736 come under the predicted toxicity class of 5 (Table 7).

Based on the high negative binding energy (least binding energy) molecular docking and pharmacokinetic properties JP-8g and REDX05358 emerged as a promising drug for the mutated plectin1a which can make functional changes in the target protein.

Table 3. Physiochemical properties of the ligand's molecules.

Ligands	MW	Fraction Csp3	TPSA	Lipophilicity
REDX05358	472.92	0.19	89.13	3.68
JP-8g	517.44	0.15	111.71	3.55
CAY10736	673.99	0.68	111.55	5.1

Note: MW: Molecular Weight, TPSA: Topological Polar Surface Area.

Table 4. Pharmacokinetics properties for Lipinski rule.

Ligands	MW	MLogP	Hydrogen Acceptors	Hydrogen Donors	MR
REDX05358	472.92	2.85	5	2	132.08
JP-8g	517.44	3.51	9	0	134.18
CAY10736	673.99	5.33	3	3	201.59

Note: MW: Molecular Weight, MR: Molar Refractivity.

Table 5. Absorption, solubility properties along with PAINS and Brenk alerts.

Ligands	GI Absorption	P-gp Substrate	Solubility	PAINS	Brenk
REDX05358	High	Yes	–5.58	0	0
JP-8g	High	No	–4.43	0	2
CAY10736	Low	No	–9.04	0	3

Note: GI: GastroIntestinal, P-gp: P-glycoprotein.

Table 6. Rotatable bonds and bioavailability score.

Ligands	Rotatable Bonds	Bioavailability Score
REDX05358	4	0.55
JP-8g	3	0.55
CAY10736	9	0.17

Table 7. Predicted toxicity class of the 3 anticancer agents.

Ligands	Class
REDX05358	4
JP-8g	5
CAY10736	5

DISCUSSION

The genetic disorder epidermolysis bullosa simplex with muscular dystrophy were reported first in 1988 by Neimi but the reason behind was unknown [1]. Mc Lean and Smith identified the affected gene as the plectin gene, which is located on chromosome 8q24 [2]. From the analysis of published plectin mutations it was confirmed that EBS-MD happens because of nonsense, insertion or deletion mutations of exon 31. Most frequently, glutamine (27% of all mutations), glutamic acid (24% of all mutations) and arginine (20% of all mutations) were replaced by other amino acids in the mutation caused by

plectin. The type of PLEC1 mutations (in-frame insertions/deletions) influences the timing of onset of muscular dystrophy and it is the skin that is the most affected among. Scaring, milia and dyspigmentation are other consequences [16]. Except dominant Ogna type EBS all mutations are recessive. This mutation happens on exons 32 and 33 [5]. When blistering occurs, it will persist mainly on the hands and face. Blistering also causes peeling of skin, erosions and ulcers will form on nail, hair, teeth, oral, and genito-urinary system leading to epidermis loss. A case study reported extreme weakness in muscles in a 29-year-old woman starting at her early 20s. There was blister formation immediately after her birth but when she grew older it disappeared. Diffuse alopecia, blisters and limb-girdle muscle weakness are seen in her as adverse effects [4].

Plectin helps in the reorganization of cytoskeleton by kinase signaling pathway [13] and expression of plectin in cells interacting with various intermediate filaments and keratins for regulate gene transcription and protein expression thereby. Exons encoding the N-terminal actin binding domain (ABD) in the isoforms of plectin in muscles exhibits higher actin binding activity than other splice exons. This mechanism based on alternative splicing is likely to boost the biological function of plectin protein as a cytolinker in striated muscle (8–10). Polymerase chain reaction (PCR) amplification detects the mutation of plectin protein followed by automated sequencing using an ABI PRISM 3130xl genetic analyzer (Applied Biosystems, Foster City, CA) [5].

The database Protein Data Bank (PDB) [1] gave the 3-D crystal structure of the protein macromolecule with its resolution with a PDB ID 4q58. It gave the method in which the crystal structure of protein is determined. To get the protein interacted with its ligand, it purified in BIOVIA Discovery Studio visualizer software. 50 drugs which are anticancer agents (ligands) already approved based on their pharmacological properties are retrieved from PubChem database. This database gave the PubChem CID and the canonical smiles (further used for ADME analysis) [1].

These ligands are imported to PyRx virtual screening software which is a computational technique for discovery of suitable drugs by obtaining the binding affinities with the protein which is converted to a macromolecule using AutoDock/AutoDock Vina algorithm. This bioinformatics tools used computational technique called molecular docking to predict the orientation of target and the ligands [1]. The AutoDock Vina stabilizes the protein and ligand, thereby, ensuring their binding. By adding torsion angles and charges each ligand molecule gives 9 confirmations when interacted with the target molecule. Therefore, for 50 drugs (ligands) 450 confirmations are obtained and we choose the ligands with best docking score. Standard free energy derivation of binding which predicts binding affinities is the result obtained from this software [4]. All the selected ligands based on this have zero RMSD values and high negative binding affinity (least binding affinity). It is considered that smaller the Root Mean Square Deviation value is the more binding the protein and the ligands will have.

The 3-D and 2-D structural interaction of 3 ligands with protein 4q58 are further visualized in BIOVIA software. This is done after selecting the 1 N compound of the ligand molecule (by excluding all the heteroatoms and other N compounds if present, as ligands are not a single fragment molecule) and pasting it upon the protein macromolecule. After getting the ligand interactions with the active sites of the receptor molecule along with the bond distance, SwissADME (absorption, digestion, metabolism and excretion) analysis was done for four ligands simultaneously [1]. ADME analysis gave the pharmacokinetics, physiochemical properties and druglike properties for the two drugs with the bioavailability radar (to get the drug-likeness). This properties of ADME tool gives the Rule-of-five called as Lipinski which says if the drugs are orally good [4]. In addition it gave the Brenk alert [5] and PAINS alert [6] which gave the number of violations if the drugs are unstable and dangerous. Two anticancer agents based on in Silico pharmacological studies were finalized as the best therapeutic targets for the drug repurposing against the mutated protein plectin 1a in epidermolysis bullosa simplex with muscular dystrophy.

As anticancer agents, these drugs JP-8g and REDX05358 selected for drug repurposing based on least binding affinity and ADME properties predicted to have good therapeutical potential against the mutated plectin 1a. The research on JP-8g as anticancer agent says it is a spirooxindole-type pyranopyrimidines which is an anti-inflammatory agent [9] (https://www.ebi.ac.uk/chebi/). REDX05358 is a novel drug which obstructs MAPK signaling in cells with tumor (as per the details given by American Association for Cancer Research in 2017). The establishment of pharmaceutical companies along with the drug repurposing has attained a better approach as it reduces the timelines of drug development [5]. It reduces the cost and risk. Repositioning of drugs needs covers approximately 30% of the newly US Food and Drug Administration (FDA)-approved drugs. More mechanism based studies are important in the alternative applications of drugs used in repurposing [4].

CONCLUSIONS

Drug repurpose in this research paper using bioinformatics databases like NCBI, PDB, PubChem, GeneCards, SwissADME along with computational software, like PyRx, which performed molecular docking, BIOVIA used for purification have implemented to therapeutically utilize the anticancer agents against the target plectin 1a in epidermolysis bullosa simplex with muscular dystrophy. It was diagnosed based on clinical, histopathological and mutation analysis of the plectin gene of the protein. As the drugs used in this attempt are having least binding affinity with the target macromolecule and satisfy the ADME properties, repositioning of these anticancer agents are taken as a lead in EBS-MD as there is no other known treatment. This lead would help the children in wheelchairs as well as with blisters on their face and mouth. JP-8g and REDX05358 proved to be best suited for the action against the protein in this disease. It is concluded from this study that drug repurposing can help in the better functioning of hemidesmosomes and helps with the interaction of intermediate filaments of cytoskeleton.

Acknowledgment

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List of Abbreviations

EBS	MD Epidermolysis Bullosa Simplex with Muscular Dystrophy
IFs	Intermediate Filaments
NCBI	National Centre for Biotechnology Information
OMIM	Online Mendelian Inheritance in Man
RCSB	Research Collaboratory for Structural Bioinformatics
PDB	Protein Data Bank
P-gp	P-glycoprotein
ADME	Absorption, Distribution, Metabolism, Excretion
SDF	Structural Data File

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