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Computational Design and Analysis of a Novel Inhibitor for *FERMT1* Gene: A Novel Treatment Strategy for the Kindler Syndrome

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Abstract

Epidermolysis Bullosa is a rare genetic condition that can lead to the blistering of the skin which appears due to a minor injury just by scratching and rubbing the skin Epidermolysis bullosa is a polygenic disorder since different types are caused by different combinations of genes. The Kindler syndrome, which is caused by disease-causing variants in the *FERMT1* (FERM Domain Containing Kindlin 1) gene, is being considered in this research. Due to the lack of a suitable drug, topical treatments have been the only option so far. Therefore, this study aims to develop a drug by the utilization of in-silico approaches to so the designed drug can act as an inhibitor and can be used to treat Kindler Syndrome. The protein of human FERMT1 gene was utilized in this study that is available under the specifically allocated UniProt ID Q9BQL6. The secondary and tertiary structure of the protein was predicted by MESSA and AlphaFold online web servers. Additionally, the ligands were designed by ELEA3D online web server and the interaction analysis was carried out utilizing the SwissDock docking server. The molecular dynamic simulation was performed by IMODs online web server to validate the results of docking. In the end, an ADMET analysis was carried out to determine the physiochemical characteristics, water solubility, toxicity, and drug-likeness of the proposed medication. It follows that a medicine developed utilizing the CAAD technique can function as an inhibitor of the Kindler Syndrome-causing gene and that if designed in vivo and in vitro, it will produce remarkable outcomes. Kindler Syndrome may one day be treatable with the help of the computer-aided medication design that has been developed.

Keywords: Kindler Syndrome, Bioinformatics, Drug Design, Inhibitor Design, Molecular Docking

1. Introduction

Epidermolysis bullosa is a genetically transmitted skin condition that has been either inherited from one of the parents who has the disease, which is autosomal dominant inheritance, or one can get the disease from both parents and that would be autosomal recessive inheritance (Mellerio, 2019). It is a rare condition that can lead to the blistering of the skin which appears due to a minor injury just by scratching and rubbing the skin (Alharthi et al., 2022). Epidermolysis has been classified into four types namely epidermolysis bullosa simplex, junctional epidermolysis bullosa, dystrophic epidermolysis bullosa, and Kindler syndrome (Boeira et al., 2013). They are distinguished by the extent of blister fragmentation and classified into several subgroups based on the genetic inheritance pattern, morphology, and topography of the diseases (Mariath, 2019). This study focuses on the *in-silico* analysis of Kindler Syndrome and the gene mutation that will

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aid in the development of a drug to treat it. A rare form of EB known as Kindler syndrome is inherited in an autosomal recessive pattern and is brought on by disease-causing variants in the *FERMT1* gene also known as the *KIND1* gene (Alharthi et al., 2022b). The symptoms of Kindler syndrome may begin to develop in young infants.

Up to now, molecular genetic engineering techniques like comprehensive genome testing or multigene paneling have been used to assess many clinical implications based on both alleles of pathogenic disease-causing variants and disease-causing variants of *FERMT1* (Youssefian et al., 2022). Photosensitivity, hyperkeratosis, Pseudo syndactyly, malignancy, mucosal involvement, poikiloderma, mucosal, variable hypermobility, and skin hyperextensibility are only some of the symptoms that have been identified in the approximately 400 patients who have been diagnosed. The gene *KIND1* that encodes kindling-1, an attachment protein for actin cytoskeleton to the matrix of basal keratinocytes, is mutated in this condition. The *KIND1* gene is likewise located on the short arm of chromosome 20. The loss of the Kindlin-1 function in this example was due to a combination of two disease-causing variants: *R271X* and *KIND1* (1755delT) (Bruckner-Tuderman, 2019). Allowing pro-inflammatory cytokines to proliferate in KS skin as a result of UV-B irradiation is proposed as a novel therapeutic method (Edrees et al., 2023). Additional studies link the actin-extracellular-matrix linker protein UNC of kindlin-1 in Caenorhabditis elegans to illness. Genetic linkage analysis and genomic screening, cell culture with RNA extraction and cDNA synthesis, multiple tissue northern blotting and cDNA panels, mutation detection, anti-kindlin antibody formation and immunohistochemistry, kindling-1 transfection, and results can be seen respectively. Clinical diagnostic criteria for Kindler syndrome have not yet been defined. Bioinformatics methods such as ELISA, immunofluorescence, flow cytometry, and PolyPhen-2 and SIFT all agreed that it is probably harmful. Therefore, this study is being conducted in preparation for the formulation of a specialized medicine based on mutational analysis, for which no recognized treatment existed previously.

Kindler syndrome is caused due to the mutation in the *FERMT1*gene at C20orf42 that encodes for the kindlin-1, a protein that is primarily expressed in keratinocytes and is an actin cytoskeleton-focal contact-associated protein (Arita et al., 2007). In individuals with Kindler syndrome, the *FERMT1* gene has been found to contain more than 70 (*FERMT1 gene: MedlinePlus Genetics*). Different bioinformatics tool have been used in this study to design the drug to treat the kindler syndrome. The first step in the drug synthesis for kindler syndrome involves the retrieval of the mutated protein encoded by the *FERMT1 (*Has et al., 2015*)*. The various physicochemical properties of the protein are then analyzed. The secondary and tertiary (3D) structures of the protein are predicted using advanced bioinformatics methods and its structural stability is scaled (Zhang et al., 2008). The tertiary structure is also refined and improved with the help of galaxy refine. As kindlin-1 is present at centrosome and it induces mitotic spindle formation its role depends on integrin binding and activation and can be identified by si-RNA. Specifically, ligand was generated from kindlin-1 by using elea3D as the targeted region will be epithelial cells for which ligand can be Ep-CAM for leukocyte associated immunoglobin like receptor and have used AutoDock vina, discovery studio and python for molecular docking and a drug can be designed according to the nature of the protein used in the specific process and PrEST – antigen as affinity ligand is used until now for affinity purification.

The Swiss Target Prediction, which forecasts the characterization of the ligand and its compatibility with its targets inside the body, was used to anticipate a drug's

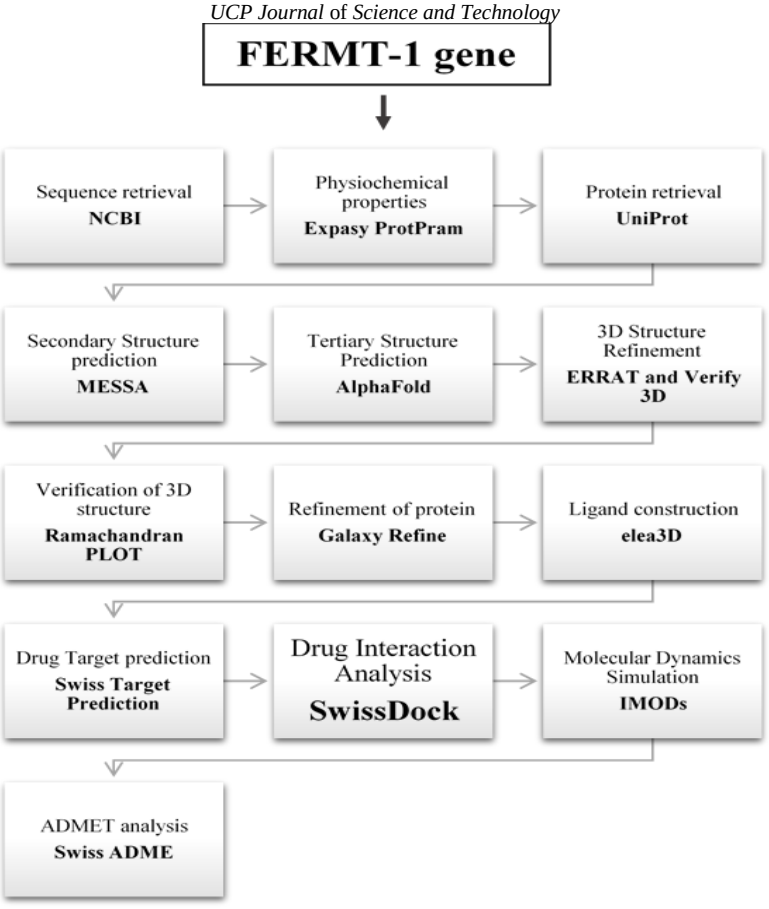

Figure 1 The methodology flow chart followed in the designing of *FERMT1* gene.

targeted locations in the following stage. The optimal docking complex was then found through docking using the SwissDock, which was afterwards recreated using IMODs. In the final step, the substance is put through additional testing to determine its many features, particularly the ADMET (chemical absorption, delivery, metabolism, excretion, and toxicity) properties. Based on how much the substance resembles a drug, an ADMET score is given to the substance. This stage brings the drug *in-silico* investigation to a close. If positive outcomes are obtained, the drug can then be *tested in vitro* and *in vivo*.

In this study, the drug has been developed using computational *In-silico* approach to treat the disease caused by the mutation in *FERMT1* gene. The kindler syndrome has never been successfully treated with a medication prior to that time. Therefore, the *in-silico* techniques used in the study has assisted in recognizing the polymorphisms of drug targets, designing the targeted drugs, binding affinity of the drug with the target and also to find out the other pathways that can get effected with the designed drug. *In-silico* drug design is cost effective in research and development of drugs (Jabalia et al., 2021).

This contemporary approach to drug development is expected to build an effective drug candidate, as it helps to analyze the molecular recognition process of targets and ligands. Nevertheless, for the effectuality and precision of the designed drug is yet to be evaluated in vivo and in vitro.

2. Methods and Methodology

This study was conducted using *in-silico* methods and protocols, the figure 1

below indicates the methodology flow chart of this study.

2.1 Sequence Retrieval

NCBI which stands for National Centre for Biotechnology Information (https://www.ncbi.nlm.nih.gov/) has been was utilized to retrieve the sequence of *FERMT1* whose NCBI reference sequence is NC_000020.11**.** The NCBI database comprises data from over 2400 species and includes over one million proteins exhibiting great biological variety encompassing prokaryotes, eukaryotes and viruses (Pruitt et al., 2005)

2.2 Physiochemical Properties

In order to get the physiochemical properties of the selected protein, the ExPaSy bioinformatics resource portal has been used which is an online tool. Expasy stands for "expert protein analysis". This portal was developed by the Swiss Institute of Bioinformatics. It provides an uninterrupted access to a large range of data in a variety of fields, including proteomics, genomics, phylogeny/evolution, systems biology, population genetics, transcriptomics, and so on (Artimo et al., 2012). ExPaSy-ProtPram is the tool of Swiss Institute of Bioinformatics(https://web.expasy.org/protparam) that was utilized to calculate the physiochemical parameters of the FERMT1 protein.

2.3 Uniprot

UniProt (https://www.uniprot.org) is the most comprehensive library of protein sequence and functional annotation, as well as the major resource for storing and combining information from huge and varied sources (Consortium, 2018). It stands for The Universal Protein Resource. Uniprot id of the protein used in this study is **Q9BQL6**. UniProt is a collaboration between the European Bioinformatics Institute , the SIB Swiss Institute of Bioinformatics and the Protein Information Resource.

2.4 MESSA

MESSA stands for MEta Server for Sequence Analysis. (http://prodata.swmed.edu/MESSA/MESSA.cgi) It is used to predict the structural and functional features of the desired protein. The server predicts the different properties of the protein such as its secondary structure, coiled coils, structurally disordered regions, signal peptides and transmembrane helices (Cong & Grishin, 2012). In this study, the input sequence of the protein is inserted in the MESSA which predicted the secondary structure of our protein.

2.5 Tertiary Structure Prediction

The tertiary structure of the protein is predicted by using the AlphaFold 2 (https://alphafold.ebi.ac.uk/) online tool. It is developed by the DeepMind which computationally predict the three structure of protein with unmatched accuracy and speed (Jumper et al., 2021). AlphaFold greatly improves the accuracy of structure prediction by incorporating novel neural network architectures and training procedures based on the evolutionary, physical and geometric constraints of protein structures.

2.6 Verification of 3D Structure

Ramachandran plot (https://swift.cmbi.umcn.nl/servers/html/ramaplot.html) gives the two dimensional plot which is used to verify the protein structure whether it is correct or not. The plot was developed in 1963 by G. N. Ramachandran. It shows the result in the form of chart with torsion angles calculated of the protein (*Ramachandran Plot - Proteopedia, life in 3D*, 2010). Two values are used one is taken on x-axis and the other on at y-axis.

2.7 Refinement of The Protein Model

Galaxy refine webserver(https://galaxy.seoklab.org/cgibin/submit.cgi?type=REFINE) is freely available online that aids in refining the structure of protein. In order to predict the structure, the need of developing template-based model structures beyond the accuracy provided by template information has been emphasized (Heo et al., 2013). Hence, the protein quality *FERMT1* was enhanced by using the galaxy refine tool.

Table 1 The composition of amino acid present in the selected protein.

Amino Acid	Number of residues	% Composition
Ala (A)	10	5.2%
Arg (R)	11	5.7%
Asn (N)	2	1.0%
Asp (D)	3	1.6%
Cys (C)	3	1.6%
Gln (Q)	10	5.2%
Glu (E)	7	3.6%
Gly (G)	23	12.0%
His (H)	12	6.2%
Ile (I)	4	2.1%
Leu (L)	24	12.5%
Lys (K)	5	2.6%
Met (M)	6	3.1%
Phe (F)	19	9.9%
Pro (P)	7	3.6%
Ser (S)	21	10.9%
Thr (T)	11	5.7%
Trp (W)	2	1.0%
Tyr (Y)	3	1.6%
Val (V)	9	4.7%
Pyl (O)	0	0.0%

2.8 Ligand Construction

Cheminformatic Tools and Databases for Pharmacology (https://chemoinfo.ipmc.cnrs.fr/) was used to construct the suitable ligand for our protein. ELEA-3D was used where protein was given as an input and got 20 different ligands out of which the model which had the highest population score was chosen as our ligand for the further analysis.

2.9 Drug Target Prediction

Swiss target prediction (http://www.swisstargetprediction.ch/) online tool had been utilized to predict the drug target. The Swiss Target Prediction engine assesses the similarity between the user's query drugs and those compiled in regulated, cleansed collections of known actives in well-defined experimental binding assays (Daina et al., 2019).

2.10 Drug Interaction Analysis

SwissDock (http://www.swissdock.ch/) is an online web server available to analyze the interaction of the designed drug with the protein. It is developed by the Molecular Modelling group and supported by the SIB Swiss Institute of Bioinformatics. The main aim of this server is to provide the protein-ligand docking that can be used to design an efficient drug. The complex with the minimum energy was selected.

2.11 IMODs

iMODS (https://imods.iqfr.csic.es/),which is an internal coordinates normal mode analysis server,contains new visualization features for depicting collective motions, such as an improved affine-model-based arrow representation of domain dynamics (**López-Blanco et al., 2014**). The IMODs server provides an easy-to-use interface for the improved NMA approach in internal coordinates.

2.12 ADMET analysis

Swiss-ADME (http://www.swissadme.ch/) is an online tool that is used to check find out the properties of the designed drug like its toxicity, excretion, absorption,

metabolism and distribution activities are checked to make sure the designed drug is safe to use. The designed drug must be capable of reaching the targeted molecule in sufficient concentration in order to carry out its biological function to either degrade or inhibit the targeted molecule (Daina et al., 2017). In this study, the ADMET score was analyzed to find out the drug like properties of the designed inhibitor.

3. Results

3.1 Sequence Retrieval

The whole sequence of the *FERMT1* gene was retrieved from the National Centre for Biotechnology (NCBI) with the accession no of NC_000020.11. The gene of the homo sapiens had been taken which was further analyzed to find the mutation which caused the Kindler Syndrome**.** The length of the selected gene has the 48186 bp.

3.2 Analysis of Physiochemical Properties

The longest open reading frame of the *FERMT1* gene was put as the input on the Expasy ProtPram which analysis the physiochemical properties of the protein. **Table 1** shows the composition of the amino acid present in the selected protein. The theoretical Pi was given to be 9.66, the point at which the pH is neutral. The aliphatic index was calculated as the 75.68 and the instability index was computed to be 35.54. GRAVY (Grand Average of Hydrophobicity) was found to be 0.011. Other physiochemical properties that were calculated by the ProtPram were the molecular weight, atomic composition, extinction coefficient, estimated the half-life of the protein in different organisms that is 30 hours in mammalian reticulocytes (in vitro), >20 hours in yeast (in vivo) and >10 hours in Escherichia coli (in vivo).

3.3 Retrieval of 3D Structure of Protein

Universal Protein Data Bank (UNIPROT) had been used to retrieve the 3D structure of the protein. Particularly Uniprot (Universal Protein Data Bank) gives in-depth useful information about the structure and function of the protein. Uniprot id: **Q9BQL6** · FERM1_HUMAN of *FERMT1* gene with *kind1* protein formation, responsible for Kindler Syndrome is analyzed. FERMT 1 has 677 amino acids. It plays significant role in adhesion of keratinocytes to fibronectin and laminin, activation of ITGA2B with talin, requires normal basal keratinocyte polarization on skin along with normal cell shape and integrin activation. It also induces keratinocyte migration to tumor site and mediates in tumor prolifer interaction with TGF –beta 1 signaling. The figure 2 below represents the 3D structure of *FERMT1* protein.

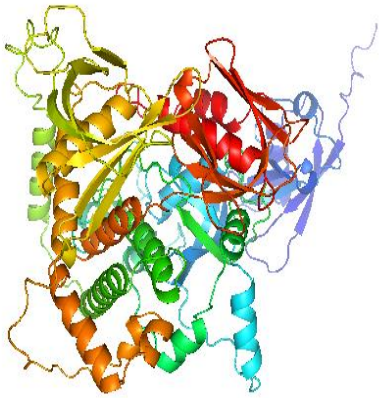

Figure 2 The 3D structure of *FERMT1* protein taken from UniProt representing the coils, helices and beta-strands in the protein structures

3.4 Secondary Structure Prediction

Another tool for structure prediction is MESSA, which have local sequence feature prediction, along with domain architecture, gene ontology terms prediction and function prediction. It also predicts Enzyme commission number and spatial structure. In this case, no EC number was not assigned to protein. It helped in predicting the secondary structure of protein and gave the score of

each residue of amino acid involved in the formation of either strand, alpha or coil.

3.5 Tertiary Structure Prediction

AlphaFold 2 was used to predict score residue along with alignments and expected position error in angstrom which provides useful information about protein folding, stability and design. Figure 3 shows the tertiary structure obtained of the protein of interest from the AlphaFold tool.

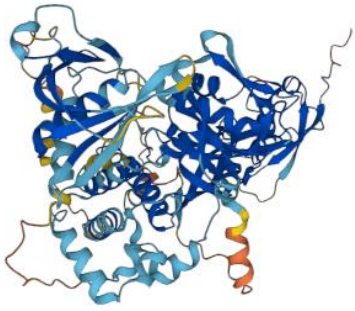

Figure 3 The tertiary structure of *FERMT1* protein obtained from the AlphaFold 2 tool

It gives the per-residue confidence score (pLDDT) which ranges from 0 to 100. Any score which is less than 50, that residue may be unstructured in insolation. The score greater than 90 is in dark blue color, the score between 90 and 70 is shown as light blue color, the score between 70 and 50 is in yellow color and less than 50 score is indicated with orange color. Given this confidence score, our most of the protein's residue had the score greater than 90 as shown in Diagram 2.

3.6 3D Structure Refinement

3-D structure can easily be refined by verify 3-D which determines compatibility of atomic 3-D model with its own amino acid sequence depending on external factors and its location (alpha, beta,loop,polar) and can compare them with good structures. ERRAT had been used in this study to check the quality of the 3D structure of the selected protein. The pdb format of the protein was uploaded and the ERRAT gave the quality factor of 92.3208. The ERRAT score greater than 90 is considered a good score.

3.7 Ramachandran Plot

Ramachandran plot explains the angles of the proteins. It gives the two-dimensional plot of all the torsion angles phi and psi that are present inside the structure of all peptides of the given protein. The plot has been typically divided into four quadrants, with three quadrants as the allowed region while the one quadrant at the bottom right is the not allowed region. The score greater than 85% is considered an outstanding one. In the study, 89.2% score was obtained of the residues that were present in the most favored region. The figure 4 below represents the Ramachandran plot for the protein of study.

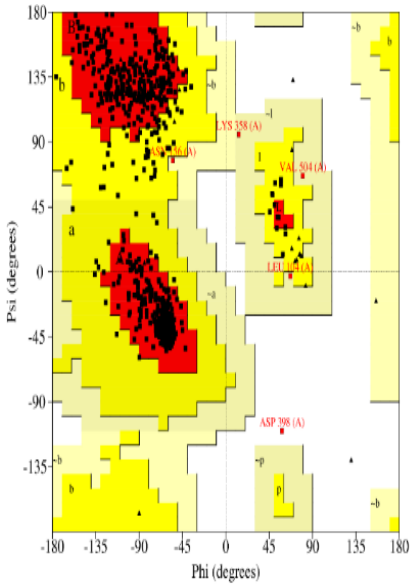

Figure 4 The results of Ramachandran plot with 89.2% of residues present in the most favored region

3.8 Refinement of the Protein Model

The degree of similarity between the target and available template structures substantially determines the quality of model structures created by modern protein structure prediction algorithms. Hence, galaxy refine tool was used to improve the model of the protein. It remodels side chains, conducts side-chain

Table 2 The ADMET properties predicted by SwissADME online tool

ADMET parameters	Parametric values
Formula	C23H25ClO4
Molecular weight	400.90g/mol
Num. heavy atoms	28
Num. arom. heavy atoms	13
Fraction Csp3	0.35
Num. H-bond acceptors	
Num. H-bond donors	1
Molar Refractivity	116.27
TPSA	63.58 Å²
Liphophilicity Log Po/w (SILICOS-IT)	7.20
Water Solubility Log *S* (ESOL)	-6.00
Class	Moderately soluble
(Pharmacokinetics) GI absorption	High
(Pharmacokinetics) BBB permeant	No
(Drug likeness) Lipinski	Yes; 0 validation
(Drug likeness) Ghose	No; 1 violation
(Drug likeness) Egan	No; 1 violation
Bioavailability score	0.55
Synthetic accessibility	4.61

repacking, and then relaxes the overall structure using molecular dynamics modeling. Out of 5 models obtained, model 2 was chosen as it had the highest score of the Rama favored with poor rotamers of about 0.2. The refined model of protein is given below in figure 5.

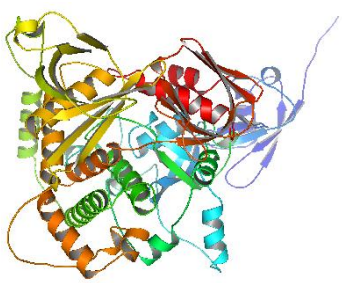

Figure 5 The Model 2 that refined by the galaxy refine online server indicating a refined protein structural model with a better quality and high Ramachandran Score

3.9 Ligand Construction

Ligand had been constructed for our selected protein *FERMT1* with the help of elea3D tool. The protein downloaded in the pdb format had been purified by utilizing Discovery Studio tool by removing water and ligand molecules. The protein had been submitted as an input in the pdb format on the elea3D and coordinates were added which were obtained from the AutoDock Vina. Twenty models were obtained, out of which 18 was the best model as it had the highest population (mean) score and it was then used as a ligand for further study. The figure 6 below represents the 3D model of the designed ligand molecule.

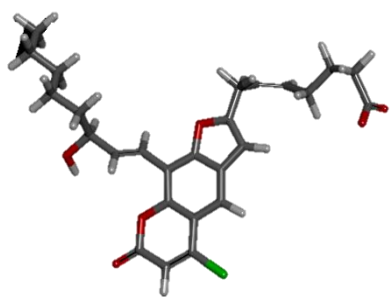

Figure 6 The selected model of designed ligand (g18 molecule) obtained from the Elea3D

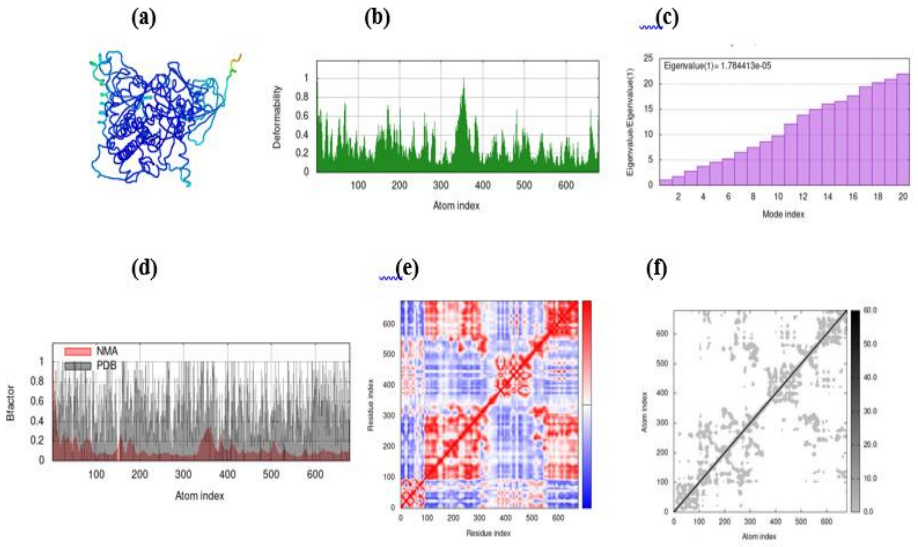

Figure 7 The results of molecular dynamics obtained via IMODs. **(a)** Stimulated 3D structure **(b)** B-factor or mobility **(c)** Eigenvalues **(d)** Deformability **(e)** Covariance map; red indicates correlated motion and blue indicates anti-correlated motion **(f)** Elastic network; the darker the color more stiffness

3.10 Swiss Target Prediction

Swiss target prediction is the tool that was used to find the compatibility and binding of the designed drug with its target. The ligand file was uploaded as an input on this tool which gave the result in the form of the pie chart. Protease are the main target of our ligand as it had the 33.3% binding capability with it followed by the kinase which had the 26.7% binding capacity with the ligand.

3.11 SwissDock

SwissDock had been used to analyze the drug interaction with the ligand. The *FERMT1* protein was uploaded in the pdb format along with the ligand in mol2 format. The docking had been run and the complex which had the minimum predicted energy **ΔG.** In our study, the complex with -10.69 kcal/mol had been downloaded and its structure had been visualized with the help of the UCSF Chimera.

3.12 IMODs

IMODs online tool had been used to run the molecular dynamics simulation of our complex to find out the changings in the protein receptor upon the binding of ligand. The eigenvalue calculated of the complex structure was 1.784413×10^{-5}. The lower the eigenvalue the more easily the protein can get deformed. The more the high peak of the B factor graph the higher are the chances of the residues to get deform. Figure 7 below represents the graphical representations of the molecular dynamic simulations.

3.13 ADMET analysis

SwissADME online tool had been used to carry out the ADMET analysis of our designed drug. The complex obtained from the elea3D had been downloaded and given as the input on the SwissADME tool. Properties like physiochemical, lipophilicity, water solubility, pharmacokinetics, medicinal chemistry and drug likeness were predicted by this tool. The table 2 represents the predicted ADMET properties of the designed ligand molecule.

Boiled egg model provides a straightforward and quick means to determine the gastrointestinal absorption and the uptake of the small molecules by the brain barrier that is associated with the drug discovery and its development. The white part of the egg represents the gastrointestinal absorption and yellow part

depicts the brain barrier having access to the molecule. In this study, the molecule 2 (*shown in red dot)* is present inside the white part. The boiled egg is shown below in the figure 8 representing the nature and absorption features of designed molecule.

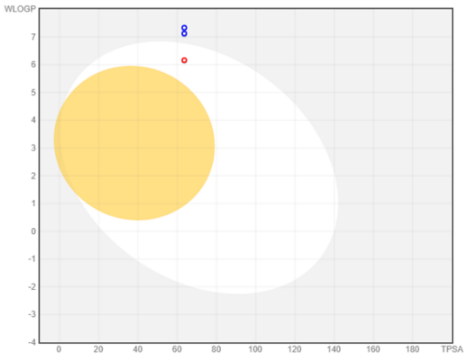

Figure 8 The image of the boiled egg retrieved from the SwissADME online *tool*

4. Discussion

The present study delves into the discipline of computational drug designing, specifically targeting Kindlin-1 associated with the *FERMT1* gene Uniprot id: Q9BQL6 (Yates et al., 2012).The method of research applied in this study involves pharmacophore modeling (Yang et al., 2010). The efficacy of any particular drug in treating Kindler Syndrome, a condition associated with disease-causing variants in *FERMT1* that result in the production of insufficient kindlin-1 protein, remains uncertain (Youssefian et al., 2022). However, ongoing research is shedding light on the root cause of the disease and potential solutions to address it. Clinical trials are presently underway to evaluate the expected outcomes for patients afflicted with Kindler Syndrome (Tabor et al., 2017).The art of computational biology was employed to develop a medicinal product through the use of pharmacophore modeling. The development of drug ligands for KIND-1 involves the utilization of both structure-based and ligand-based techniques (Has et al., 2011). Through the utilization of a structure-based approach, one can identify potential ligands by docking compounds and subsequently determining the interactions between the receptor and ligand (Yates et al., 2012). The present study encompasses advanced bioinformatics and technological methodologies to offer mankind a potential cure for Kindler Syndrome. The FASTA format of the Kindler Syndrome *KIND 1* mRNA cds with accession NC_000020.11 has been retrieved from NCBI, containing the protein sequence. The physicochemical properties of the protein were cautiously analyzed using ExPASy ProtPram. This involved a thorough examination of the amino acid composition, molecular weight, extinction coefficient, estimated half-life, and theoretical Pi, which was determined to be 9.66. With a calculated aliphatic index of 75.68 and a computed instability water index of 35.54. The grand average of hydrophobicity was determined to be 0.011.The Universal Protein Data Bank (Uniprot) was utilized to forecast the three-dimensional configuration of the protein, which provided comprehensive insights into its structure and functionality. The *FERMT1* gene, specifically *FERM1*_human, which is responsible for Kindler Syndrome, has been subjected to analysis. This particular gene is comprised of 677 amino acids. The adhesion of keratinocytes to fibronectin and laminin, as well as the activation of ITGA2B with talin, are of great importance (Ussar et al., 2008).For the skin to maintain its optimal state, the basal keratinocytes must exhibit proper polarization, with cells maintaining their natural shape and integrin activation. The prediction of a protein's secondary structure is facilitated by MESSA, which provides a score for each amino acid residue. This score offers valuable insight into the protein's spatial arrangement and enzyme commission number. In addition, it furnishes prognostications for sequence and function characteristics, as well as domain architecture and gene ontology. The protein under study has not been assigned an Enzyme Commission number.

The Alpha Fold 2 has successfully predicted the tertiary structure of a protein, providing valuable insights into the scoring residue, alignments, and expected position error. This information is crucial in determining the protein's folding, stability, and design. The algorithm provides a per-residue confidence score, revealing that a significant majority of the protein's residues received a score exceeding 90. The process of refining the 3-D structure involves the verification of its compatibility with the atomic model and its amino acid sequence, considering external factors and its specific location. The protein's PDF format was successfully uploaded, and its quality factor was determined to be 92.3208 by ERRAT. In our study, we employed the Ramachandran plot to analyze the distribution of residues. The results were quite promising, with a remarkable 89.2% of the residues found to be situated in the most favored region. It elucidates the various angles of proteins, accompanied by a two-dimensional plot of the torsion angles phi and psi that comprise the structure of the protein in question. The refinement of the protein model was carried out using the Galaxy refinement tool, which is a cutting-edge protein structure prediction algorithm. Among the five models that were procured, the second model was deemed most suitable, given its superior score of the Ramafavored with poor rotamers, which amounted to approximately 0.2. The construction of the ligand for *FERMT1* was executed utilizing the ELEA 3D tool. The input for ELA 3D includes the protein in pdb format, along with the coordinates from auto dock vina. Out of a pool of twenty models, the most exceptional was discovered. With the highest population or mean score, this particular model was selected as the ligand for further investigation. The Swiss Target Tool was employed to ascertain the compatibility of the proposed medication with its intended target. Upon uploading the ligand file, the outcome was presented in the form of a pie chart. Our ligand primarily targets proteases, given their binding capacity of 33.3%, while kinases exhibit a binding capacity of 26.7% with the ligand. The Swiss dock is employed for the analysis of drug interaction with ligands. The PDB format of the *FERMT1* protein, along with its corresponding ligand, was uploaded. The complex boasting a remarkable -10.69 Kcal/mol was procured for our study and subsequently rendered in visual form with the aid of UCSF Chimera. The IMODs online tool was employed to conduct a molecular dynamics simulation of our complex, to elucidate the alterations in the protein receptor that occur upon ligand binding. The computed eigenvalue of the intricate structure amounted to 1.784413 * 10^-5. The Swiss ADMET online tool was employed to conduct an in-depth analysis of the ADMET properties of our newly designed drug. This included the prediction of various crucial parameters such as physiochemical attributes, lipophilicity, water solubility, pharmacokinetics, medical chemistry, and drug-likeness. The intricate structure derived from ELEA3D is submitted as input within the SwissADME tool. Within the confines of our investigation, it has been determined that the molecule denoted as 2 is situated within the albumen of a boiled egg model. Within the confines of this study, a diminutive molecule was employed to fashion a medicinal substance. The ligand adjoined itself to the protein of concern, and the molecular recognition of targets was scrutinized in depth (Prieto-Martínez et al., 2019).The utilization of *in-silico* approaches in the study has proven to be advantageous in the identification of drug target polymorphisms, development of targeted medications, analysis of ligand interactions with proteins, and exploration of potential pathways affected by the created drug. The initial phase in the development of medication for Kindler syndrome necessitates the retrieval of the mutant protein generated by the *FERMT1* gene. The various physicochemical

characteristics of the protein are then scrutinized. The alignment of the principal sequences of kindlin was accomplished through a thorough blast search, as detailed by Kloeker et al. in 2004. Various instruments are employed in the process of drug design. Over seventy disease causing variant have been unearthed in the *FERMT1* gene among individuals afflicted with Kindler syndrome. Recent advancements in molecular modelling techniques have enabled the application of computer-assisted drug design in the quest for novel mechanism- or structure-based medications.ssss The present study employs a non-testing methodology, which has yielded results of remarkable precision. As such, it holds great promise in the realm of disease treatment. The novelty of the subject matter renders it advantageous, for it remains untouched by previous inquiry. Although scant research has been conducted, regrettably, no remedy exists to alleviate its symptoms. The drug in question exhibits promising efficacy in the treatment of Kindler Syndrome, as evidenced by in vitro studies conducted (Fatima et al, 2021). Prior to utilization, pre-clinical testing is conducted to ascertain that the medication possesses all the requisite characteristics or attributes. Its role in the advancement of technology cannot be overstated, and it is also a highly effective method for treating complex diseases. Its contribution to the progression of technology is noteworthy, and it also serves as a promising approach to addressing intricate medical conditions.

5. Conclusion

Epidermolysis bullosa is a hereditary condition that manifests in four distinct forms. The subtype of this disorder that was examined in this study was Kindler Syndrome. This condition results from a -disease-causing variant in the FERMT 1 gene and is extremely rare. Unfortunately, the only effective long-term solution now available is the topical cream. As a result of this scientific understanding of the Kindler Syndrome-causing gene mutation, a targeted, particular medication was designed *in-ssilico* using several bioinformatics tools. To build a medication that can inhibit the *FERMT1*, the most effective ligand was selected and interacted with the protein. The potential to deliver enrichment in identifying molecules and genes for the target of interest is increasingly being demonstrated by these methods, and while they have not yet been confirmed to develop drugs on their own, they do represent progress. However, additional analysis of the development.

6. Declarations

6.1 Conflict of Interest

All authors declare that they have no conflict of interest.

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