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STRUCTURE-BASED VIRTUAL SCREENING STUDY OF FDA-APPROVED DRUGS TO INHIBIT TP53 72 ARG/PRO VARIANT IDENTIFIED IN ACUTE LYMPHOCYTIC PATIENT VIA WHOLE EXOME SEQUENCING

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Abstract
Acute lymphoblastic leukaemia (ALL) is a significant threat to global health. Tumour suppressor gene TP53 mutations are often associated with a more aggressive form of leukaemia and poorer prognoses. This study conducted whole-exome sequencing of leukaemia patients at various treatment stages, including early diagnosis, relapse, and remission. We identified a missense 72 Arg/Pro (rs1042522) homozygous and heterozygous variant along with indel novel intron variant 376-158delAAAAAAA and 993+409delT in TP53. This mutational profile may serve as a predictor of poor treatment success in the Pakistani Pathan (Pakhtun) Population. Theoretical study explores the virtual repurposing of the FDA-approved drugs as inhibitors against these mutant TP53 cancers. The crystal structure of the TP53 proteins was downloaded from Alpha fold database and PDB and subjected to virtual screening by the DrugRep web server while using an FDA-approved drugs library as a ligands database. Our study revealed that Duvelisib and Robinin herb are the top-ranked inhibitors of MUT TP53 as compared to the reference chemotherapy. Duvelisib exhibited a docking score of −10.6 kcal/mol while Robinin herb scored –10.4 kcal/mol. In conclusion the two drugs deserve further consideration as possible cancer treatment option.

Key words: TP53, Messense Mutation, Acute lymphocytic leukemia, Docking.

Introduction

The malignant transformation and multiplication of lymphoid progenitor cells in the bone marrow, blood, and extramedullary locations are known as acute lymphoblastic leukemia (ALL). ALL is the most common malignancy in children and causes 25% of adult cases of acute leukemia (1) B-ALL the B-cell precursor is a lymphoid progenitor cell cancer that exhibits significant biology and clinical variability (2). Adults are more prone than children to develop high-risk B-ALL disease, and despite aggressive chemotherapy and/or allogeneic stem cell transplantation therapies, adult long-term disease-free survival rates are only 40%. This stands in stark contrast to pediatric ALL, where advanced treatment protocols have led to cure rates that are close to 80% ((3). Nevertheless, despite this success, some children with ALL have a dismal prognosis; 15% of them die from ALL relapses (4) Pakistan has one of the highest infant mortality rates in the world, at 71% (5).

Clinical, haematological, and genetic factors, such as age, leukocyte count at diagnosis, percentage of blasts in peripheral blood, immunophenotype, central nervous system involvement, cytogenetic and molecular alterations, and the presence of minimal residual disease (MRD), have been the focus of prognostic research for B-ALL. The latter two characteristics are the ones most strongly linked to prognosis (6). However, in 30% of pediatric ALL patients and 50% of adult ALL patients, there are no clear genetic markers of biological and clinical importance. Each genetic subtype contains hidden mutations that are powerful independent indicators of outcome and are recognizable as somatic mutations in lymphoid malignancies (7).

Next-generation sequencing (NGS) technology has significantly improved the ability to identify somatic mutations in B-ALL in both children and adults. These mutations affected genes involved in RAS signalling (48%; for example, NRAS, KRAS, PTPN11, FLT3, BRAF, and NF1), B-cell differentiation and development (18%; for example, PAX5, IKZF1, EBF1, VPREB1), JAK/STAT signalling (11%; for example, JAK1, JAK2, IL7R, and CRLF2), cell cycle regulation and tumour suppression (6%; for example, TP (9%, e.g., ETV6, CREBBB, and TBL1XR1) (8) The prognostic significance of these mutations as indicators of clinical trajectory, result, and therapeutic response are still being investigated. The frequency and clinical significance of somatic mutations in a bespoke panel of six genes, including TP53, JAK2, IL7R, PAX5, LEF1, and CRLF2 exons are targeted exonic areas are known to be hotspots for mutations.

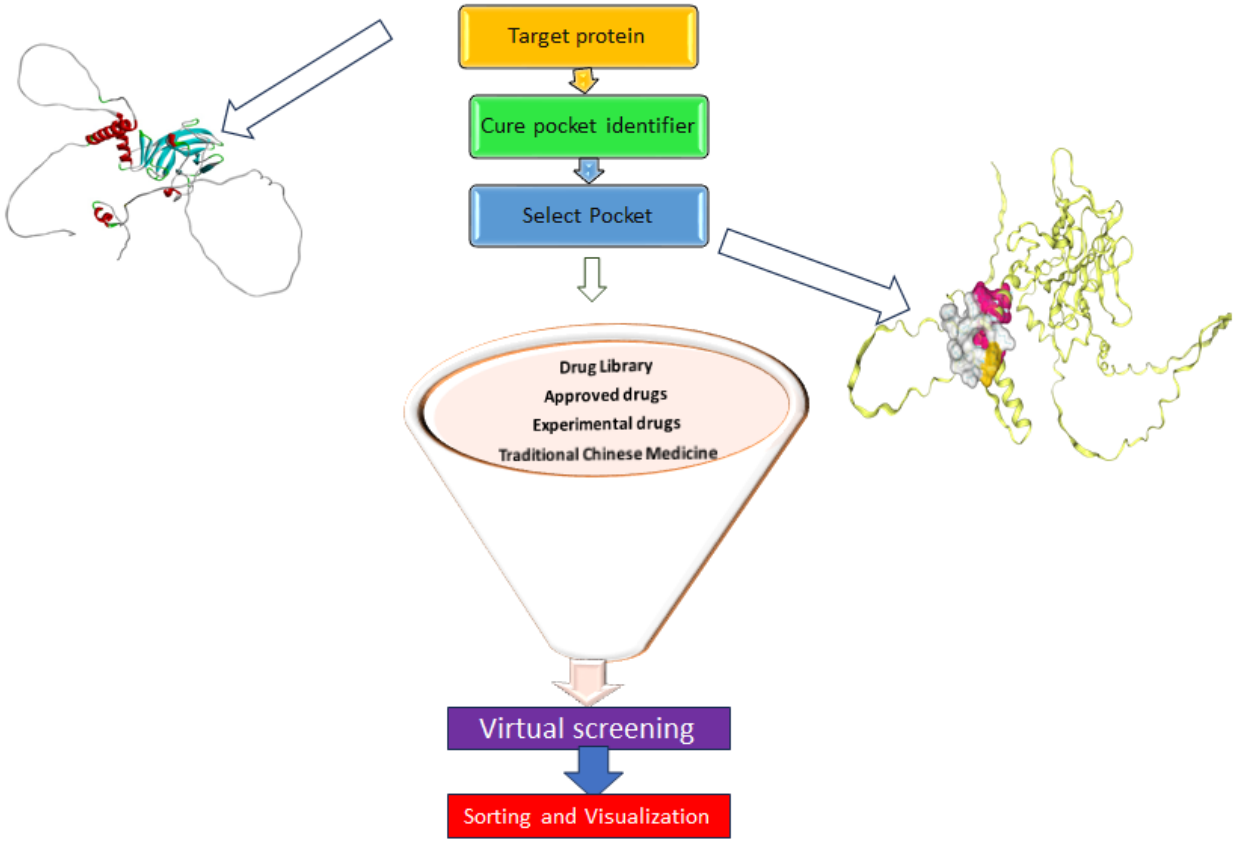
Here we show for the first time in six patients from the Pathan (Pakhtun) ethnicity of Pakistan, that TP53 mutations adversely affect the prognosis of paediatric patients. This affirms their function as predictive biomarkers and proposes that, if determined at diagnosis, they can help B-ALL patients be appropriately categorized according to their risk.

Using computational methods like molecular docking, which have grown in importance as drug discovery tools, this study provides a quick and affordable means to screen a large library of FDA-approved medications and find possible candidates for inhibitory activity against MUT TP53 compared to the used reference chemotherapy. Finding possible candidates who exhibit dual inhibitory capabilities against Mut TP53 is facilitated by this process. A basic feature of docking is important because molecular docking techniques can search through large databases for hit detection and new small molecule design (9) (10)

Duvelisib, also known as IPI-145 and INK-1197, is a phosphoinositide-3 kinase small-molecule inhibitor. Its original purpose was to demonstrate that the concurrent inhibition of the isoforms delta and gamma might result in a wide inhibitory effect on innate immune cells and adaptability. Duvelisib has demonstrated throughout its development as a powerful inhibitor of both types. FDA authorised duvelisib on September 24, 2018, after it was created by Verastem, Inc (11).

It might provide a personalized medicine approach by customizing known medications for individual patients based on their distinct therapeutic requirements and molecular profiles.

Flow chart of structure-based drug discovery and Silico analysis



Material and methods

Sample collection:

Paediatric leukaemia patients are children diagnosed with leukaemia between the ages of 2 and 16 who are undergoing treatment. A peripheral blood sample of 2 millilitres was drawn from each patient. Peripheral blood was obtained and stored at -20 °C in vials coated with EDTA to isolate DNA.

DNA isolation and whole exome sequencing

DNA was isolated from whole blood using QUBIT DNA BR, with minor modifications made to the manufacturer's instructions. The sample integrity and quality of the isolated DNA were tested using Agarose Gel Electrophoresis, which involved a 1 percent Agarose Gel Concentration, 150 V of voltage, and 40 minutes of electrophoresis time.

WES data analysis

Seven samples were used in the Whole Exome Sequencing study. One sample from a normal, healthy child, two samples from patients in remission, two samples from patients experiencing a relapse, and two samples from patients receiving initial diagnoses were all sequenced. The Short-Insert library type was used. The read length of the sequence, PE100 Clean Fastq Phred with quality score encoding, was determined by using DNBSEQ as the sequencing platform (12). This work utilized the Agilent V5 Exome kit and the reference genome version hg19.

Bioinformatics Analysis Overview

With the sequencing data, bioinformatics analysis got underway. First, data filtering on raw data resulted in the production of clean data or clean reads. Then, to create a preliminary comparison file in BAM format, the entire set of clean data from each sample was mapped to the human reference genome. Software called Burrows-Wheeler Aligner (BWA) was employed to perform the alignment. We used the Genome Analysis Toolkit's recommended Best Practices for variant analysis to ensure reliable variant calling (GATK). GATK was used to mark duplicate reads and recalibrate the base quality score. Based on the alignments, the depth and coverage of everyone's sequencing were computed. Additionally, a comprehensive data analysis quality control system (QC) was implemented into the entire pipeline to ensure accurate sequencing data. Based on the alignments, the depth and coverage of everyone's sequencing were computed. To ensure accurate sequencing data, a comprehensive data analysis quality control system (QC) was built into the entire workflow. SNP and InDel were found using cutting-edge tools, like GATK's Haplotype Caller (13). The filtering process was then used to obtain variant calls with a high degree of confidence. The SnpEff program was then used to execute a series of annotations for variants (**http://snpeff.sourceforge.net/SnpEff** manual.html). Cancer susceptibility genes, driver gene clones, drug-targeted annotations, high-frequency mutations, homology, hyper-mutate samples, loss of heterozygosity, molecular categorization, mutation signals, and neoantigen prediction analysis are some examples. Use CNVnator to identify copy number variation in the genome CNV, BreakDancer to identify structural variation in the genome SV, and Ensemble-VEP to annotate the SV/CNV results (14)We performed cancer susceptibility genes, driver gene clone, drug targeted annotation, high-frequency mutation, homology, hyper mutate sample, loss of heterozygosity, molecular classification, mutation signals, and neoantigen prediction study as part of the advanced analysis(15)

Structure prediction and validation

Uniprot ID: P04637and crystal structure from PDB ID 8F2H were used as a guide to forecast the 3D model of TP53, protein using the Alpha fold database and PDB. Mutant models were produced using Chimera 1.16 by substituting an amino acid at a specific position (72). The structural data were refined by using the Galaxy refined software and verified by using Saves 0.6. The Ramachandran plot analysis proved that 95% of the residues and mutant protein structures were present in the regions where torsion angles are allowed. The overall quality factor of the structural models for both wild-type and mutant, as assessed by Errat, was 96.2%.

Receptor preparation for virtual screening

This study focused on TP53 which was suppressed. The target protein TP53's experimentally determined 3-D structures were obtained from the Protein Alpha Fold Database an PDB. The polar hydrogen atoms and other missing atoms were added to the target protein structures, co-crystallized water and heteroatoms were eliminated, partial charges were assigned, and their energies were reduced by using the conjugate gradient and steepest descent algorithms of UCSF Chimaera v1.1622. Given that the Mut tp53 structure chain A pocket 1 was chosen for docking.

Ligands library preparation for virtual screening.

The FDA-approved drug library is used for the creation of ligand libraries. The structured data file (SDF) format including all the FDA-approved drug compounds has been downloaded from Drugs Bank (https://go.drugbank.com/) (16). FDA-approved therapeutic compounds' structures were energy-minimized and prepared for virtual screening as ligand libraries. We chose this collection intending to do drug repurposing of drugs approved by the FDA.

Virtual screening

The newly created server DrugRep carried out the virtual screening in this instance. The AutoDock Vina algorithm is used by DrugRep, a programmed and parameter-free online virtual screening server, to dock multiple ligands and rank the best-fitting conformers of molecules by calculating the docking score, binding conformation, and binding affinity between the receptor and ligand structures. (17)The absorption, distribution, metabolism, and excretion (ADME) characteristics of the main ligands are predicted by this website, among other pharmacodynamics services26 (18). The previously created FDA-approved drug library, which comprises distinct drug compounds (http://cao.labshare.cn:10180/DrugR ep/php/index.php) was subjected to structure-based virtual screening of the receptors' pre-existing structures during the DrugRep virtual screening (19).

Mut TP53 receptor docking grids were created throughout the docking process. The mut TP53 docking grid was sufficiently expanded to encompass nearly all of the binding site residues of pocket 1, such as residues ASP352, LYS292, HSD296 GLY356, GLN354, LYS357, GLU326 LYS291 LEU350, GLY293 TYR327, ASP324 ASN288 ALA353 LEU323 ALA355 PRO295 GLU287 GLY325 GLU349 GLU294 ARG290 HSD297, and THR324.

Receptor–ligand complex analyses.

With the help of Discovery Studio Visualizer 2022, the pattern of interactions between the receptors and the top-ranked drugs was clarified. The interactions, binding conformation, and binding affinity (docking score) of both receptors in complex with their respective ligands (drug molecules) were examined. The complexes were also examined for their pharmacokinetic properties, which included their molecular weight, the number of donors and acceptors of hydrogen bonds, and their LogP values (Lipinski's rule of five). Based on their optimal docking score, pharmacokinetics, and pharmacodynamics characteristics, the best-fitting ligands were chosen based on their binding affinity.

Results

Clinical characteristics

Seven samples—two from patients diagnosed at the beginning stage, two from patients in remission, two from patients experiencing a recurrence, and one from a healthy child—were chosen for Whole Exome Sequencing (WES). With a few exceptions for remission samples, the individuals that were chosen had blast cells greater than 20%, a high leukocyte count, and poor haemoglobin. Weakness, fatigue, lethargy, dyspnea, fever, weight loss, or bleeding were among the clinical signs. Blasts invading organs or lymph nodes may potentially result in adenopathy or hepatosplenomegaly. It is unclear how many Pakhtun-ancestry youngsters in Pakistan have ALL and what their prognosis is.

Using WES, we found an average of 106,442 SNPs; of these variants, 92.71% were annotated in the 1000 Genomes Project database, and 98.27% were represented in dbSNP. 1,812 novel SNPs were found, and their Ti/Tv (transversion to transition ratio) was 2.32.

Prediction and visualization.

A missense 72 Arg/Pro (rs1042522) homozygous and heterozygous variant along with indel novel intron variant 376-158delAAAAAAA and 993+409delT heterozygotes identified in TP53. This mutational profile may be a prediction of poor treatment success in the Pakistan Pathan (Pakhtun) Population. The results from various computational tools, including FATHM, SIFT, Polyphhen2, Mutation ASSESSOR, and META SVM, indicate the presence of a missense mutation (rs1042522) in all six samples analysed in this study. This mutation is located on chromosome 17 and spans from codon 7579472 to codon 7579472, resulting in the Pro72Arg substitution. Previous research has suggested that Pro72Arg (rs1042522) is associated with poor treatment outcomes in relapse

patients. However, in this study, the mutation was also found in the remission samples, and both homozygous and heterozygous forms were observed in patients, as presented in [Table 3.8].

In addition to the missense mutation, this study also identified two intronic variants: 376-158delAAAAAAA at position 7578711 and 993+409delT at position 7576443, both in heterozygous form. It is well-established that intronic mutations can affect the stability of the Tp53 protein and consequently impact its growth-suppressive properties.

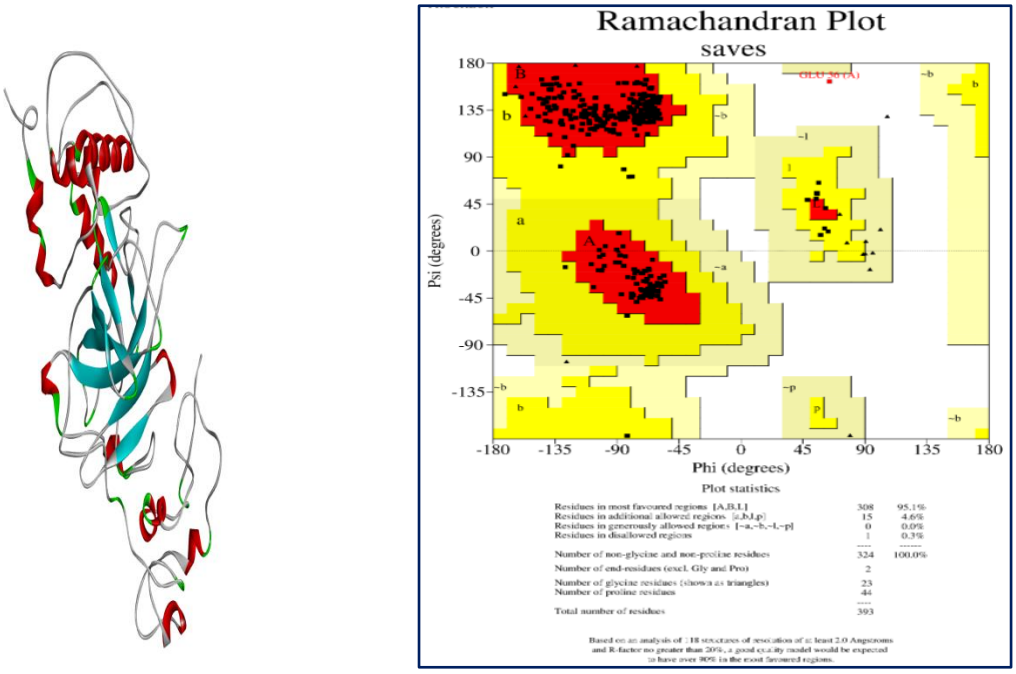


Figure 1. Show 3D structure of TP53 mutant proteins, in solid ribbon style (red: alpha helix, blue: beta sheets, grey: coils, green: turns) (B) Illustrates a Ramachandran plot of the TP53 protein structure model.

Table 1: Tp53 missense variants dbSNP rs1042522

Function	Missense variant
Gene	TP53
Exonic|Biotype	MISSENSE
Codon Change	cCc/cGc
Transcript	NM_000546.5: p. Pro72Arg/c.215C>G
PREDICTION	Cancer
FATHMM	-5.23, (Damaging)Cancer
SIFT	0.262,0. (Tolerable)
PolyPhen2	0.0,0.128, (Benign)
Mutation Assessor	1.355(L)
Other info	Het/ homo

Het* Heterozygous, Homo* homozygous

[Table 1] displays the prediction scores of rs1042522 using various tools such as FATHMM, SIFT, Polyphen 2, and Mutation Assessor to assess the deleterious effects of TP53 gene variants. According to these scores, rs1042522 is predicted to have a moderate impact on protein-coding. The table [Table 2] includes information about intron and 3 prime UTR variants detected in the protein-coding region of the TP53 gene. These intron variants were found in all patient samples, regardless of their diagnosis status (early diagnosis, relapse, or remission). Also, other variants such as

rs2909430, rs1642785, and rs1625895 were prevalent across all patient samples. Further research may be required to determine the functional effects of these variants on the TP53 gene.

Table 2: TP53 novel indel variants in early diagnose patients and missense variants in relapse and remission patients.

Function	Exonic|Biotype	Transcript	dbSNP ID	Start	End	
intron_variant	protein_coding	NM_000546.5: c.993+409dupT	Novel	7576443	7576443	Het
intron_variant	protein_coding	NM_000546.5: c.376-162_376-158delAAAAA	Novel	7578711	7578711	Het
intron_variant	protein_coding	NM_000546.5: c.993+408_993+409delTT	Novel	7576443	7576443	Het
3_prime_UTR_variant	Protein_coding	NM_000546.5: c.*184T>C	Novel	7572743	7572743	Het

Het* Heterozygous.

Silico analysis structure-based drug discovery

Virtual screening of the FDA-approved drug library which contains 2315 different drug molecules (http://cao.labshare.cn:10180/DrugRep/php/index.php) was carried out by the DrugRep server. According to our docking results, Duvelisib and Robinin Chinese herb strongly bonded to TP53 and obtained the lowest docking score (−10.6 kcal/mol and 10.4 kcal/mol respectively) (Table 3 and 4). The docking score of the top-10 drugs was −10. to −10.4 kcal/mol in the active site of TP53, which reflects their high binding energy towards TP53. To Lipinski's rule of five (RO5), all the mention ligand is already FDA-approved.

The remaining drugs could strictly follow the RO5. Overall, as compared to the reference compound of tp53, all the top-10 drug candidates exhibited high affinity towards the TP53. According to our docking results, Duvelisib and Robinin strongly bonded to TP53 and obtained the lowest docking score (−10.6 kcal/mol and –10.4 kcal/mol). The docking score of the top-10 drugs was −10.6 and the Chinese herb robinin is −10.4 kcal/mol in the active site of TP53, which reflects their high binding energy towards the Mut TP53. To Lipinski's rule of five (RO5).

Docking result of mut tp53

Table 3. Binding affinities and Lipinski's five of the top fifteen Mut inhibitors rule. Molecular weight (MW), rotatable bonds (RB), and hydrogen bond donors (HBD) and acceptors (HBA).

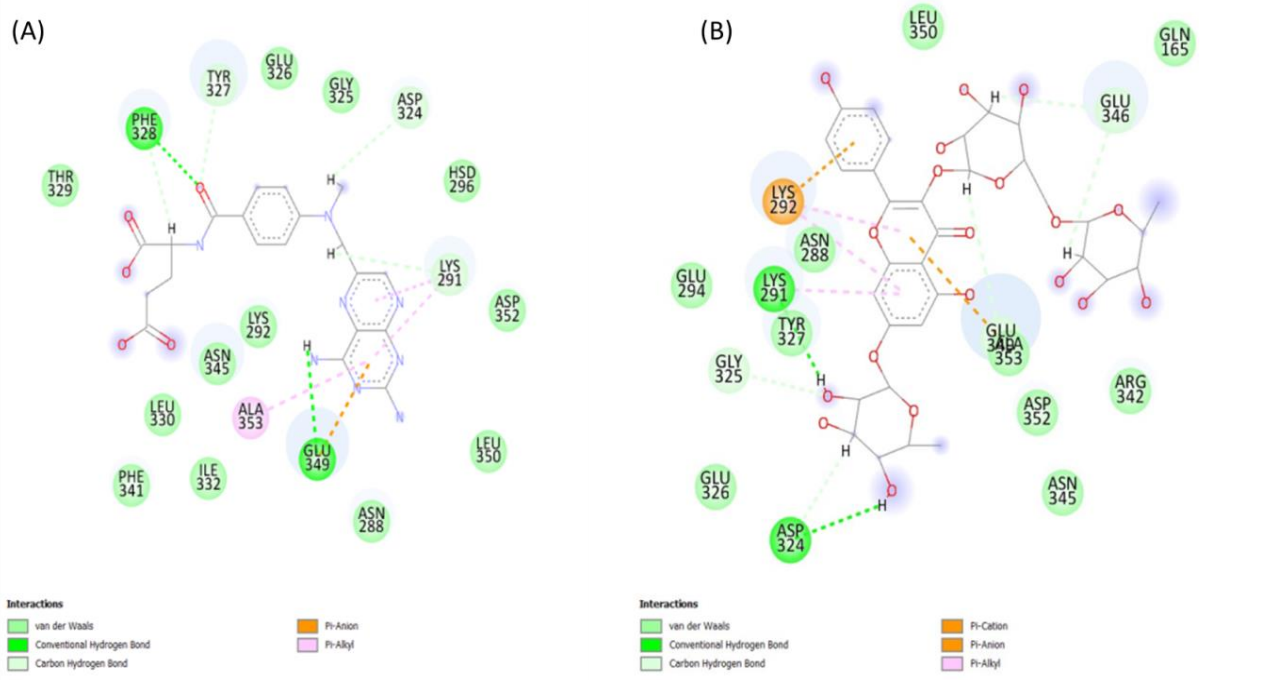
Name	Score	MW	HBD	HBA	RB	Rings	LogP
Duvelisib	-10.6	416.87	1	4	4	5	5.4
Tucatinib	-10.3	480.532	2	4	6	6	3.9
Conivaptan	-9.9	498.5744	1	3	6	6	5.6
Tazemetostat	-9.9	572.75	1	2	10	5	6
Telmisartan	-9.9	514.6169	1	4	8	6	6.9
Idelalisib	-9.8	415.432	1	5	5	5	4.9
Olaparib	-9.7	434.4628	0	4	6	5	3.5
Lumacaftor	-9.6	452.414	2	4	7	5	4.4
Lifitegrast	-9.5	615.48	2	6	10	5	4.6
Dabrafenib	-9.5	519.562	2	5	6	4	4.7
Simeprevir	-9.4	749.939	2	7	9	7	4.8
Vincristine Reference	-7.15	824.95	3	12	10	9	2.82
Methotrexate Reference	8.86	454.4	5	12	9	3	-1.8

Table 4. Binding affinities as well as Lipinski's rule of five of top-10 Mut TP53 inhibitors (herbs). MW molecular weight, HBD hydrogen bond donor, HBA hydrogen bond acceptor, RB rotatable bonds.

Name	SCORE	MW	HBD	HBA	RB	RINGS	LOGP
Robinin	-10.4	740.66	11	12	19	6	-2.8
Mulberroside C	-9.4	458.46	5	5	8	5	1.5
Nicotiflorin	-9.4	594.52	9	10	15	5	-1.5
Mudanpioside C	-9	600.57	5	7	15	7	0.3
Veratramine	-9	409.61	3	2	4	5	4.3
Scutellarin	-8.9	462.37	7	9	11	4	0
Naringin	-8.9	580.53	8	9	14	5	-0.5
Corylifol A	-8.9	390.47	2	3	8	3	5.4
Tetrahydrocoptisine	-8.9	323.34	0	0	0	6	2.9

Receptor–ligand interaction analyses.

Our study shortlisted the top 10 drug molecules that have obtained the lowest docking score with TP53 [Table 3 and 4]. The interaction analyses of the top-2 drugs suggested that A reference methotrexate formed two hydrogen bonds with Phe 328 and Glu 349, drug B Robinin formed two Vander Waals bonds with Tyr 327 and ASP 324, while five conventional hydrogen bonds. The drug Duvelisib C show hydrogen bonds with ASP352, and TYR327and vander wall interaction with HSD 296, while vincristine D show four carbon hydrogen bonds interaction [Fig. 2]. Apart from polar interactions (hydrogen bonds), all the three drugs also established an extensive nonpolar (hydrophobic) interactions network with several residues of the tp53 binding pocket [Fig. 3].



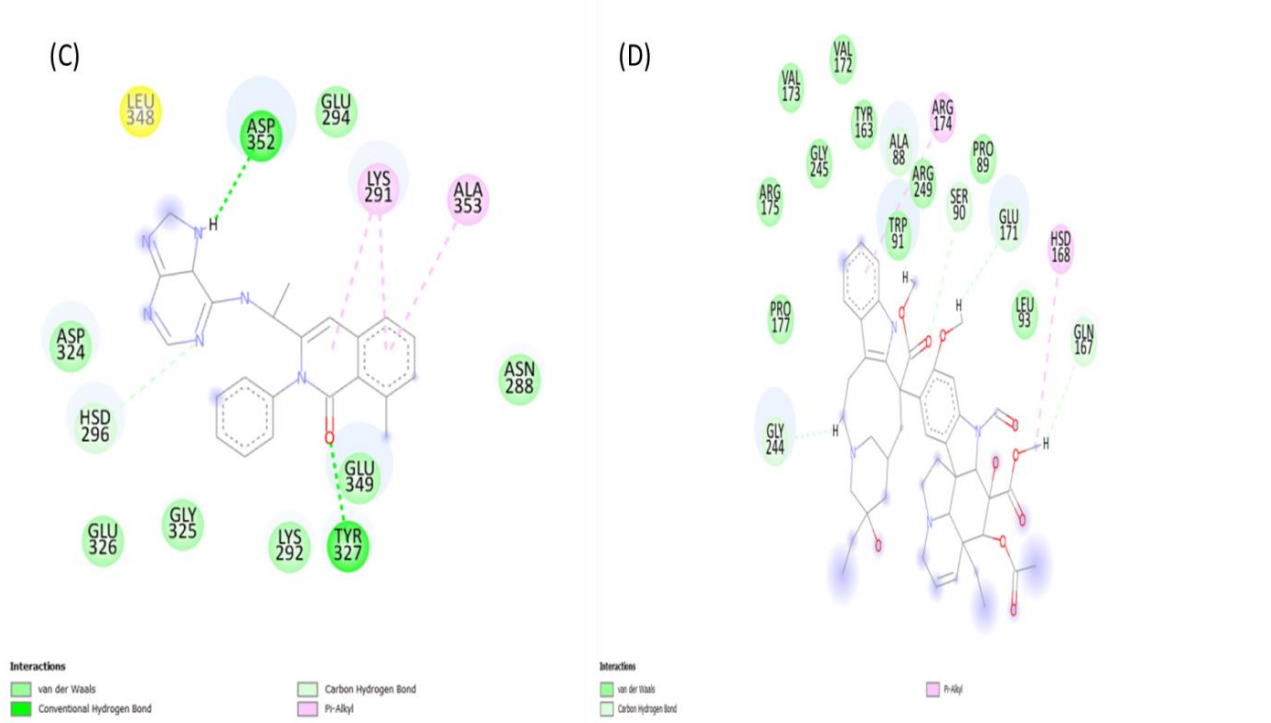


Figure 2: Discovery Studio's visualisation of the receptor-TP53-ligand interaction pattern. The top two Mut TP53 inhibitors are indicated by (B) robinin herb and (C) Duvelisib, while the reference inhibitors methotrexate and vincristine are indicated by (A) and (D), respectively.

Discussion

The preference of *TP53* variants, in all treated patients as detailed in [Table 1] raises concerns about their role in poor treatment responses. Mutations identified in whole exome sequencing of acute lymphocytic leukaemia patients at diagnosis are well documented in acute lymphocytic leukemia patients (20), highlighting the leukaemia hotspots in these altered exons. The recent study reports a SNP on chromosome 17 denoted as Pro72Arg. previous research linked Pro72Arg (rs1042522) to unfavourable treatment outcomes in all relapse patients. In our study, the variant is also reported in the remission samples in both homozygous and heterozygous forms observed in patients Additionally intronic two novel indel intronic variants 376-158delAAAAAAA at position 7578711 and 993+409delT at position 7576443 heterozygotes were identified [Table 2]. It is widely acknowledged that intronic mutations impact the Tp53 protein's stability and, effecting, its growth-suppressive properties.

According to our investigation, TP53 Mut is frequently found in B-ALL relapse patients. TP53 tumour suppressor gene plays a vital role in controlling the cell cycle and triggering programmed cell death after DNA damage. With well-established significance in carcinogenesis in both solid and haematological malignancies (21). Previous research has consistently linked TP53 mutations was to worse outcomes in children, chemoresistance and a worse prognostic effect in many tumours (22) (23) The importance of TP53 sequencing at the time of diagnosis is underscored by our findings and existing evidence. Whole exome sequencing (WES) conducted in our study revealed the presence of a missense mutation (72 Arg/Pro, rs1042522), and a novel indel variant (376-158delAAAAAAA and 993+409delT). Our findings suggest that TP53 should be closely examined at the time of diagnosis, especially in patients from Pakistan, where the mortality rate of B-ALL is higher than in other parts of the world. Deep sequencing may prove to be a useful tool in guiding treatment decisions for patients with TP53 mutations and may lead to the development of alternative therapeutic options. In summary, further investigation is needed to fully understand the implications of these results and to develop more effective diagnostic and treatment strategies for B-ALL patients with TP53 mutations.

The study also revealed that several FDA-approved medications can take the place of the reference TP53 inhibitor because of their higher binding affinities. The top ten drugs' ADME characteristics suitably fulfil Lipinski's rule of five. The fit to the active site with the formation of multiple H-bonds, which accounts for the stronger binding affinity, was revealed by the detailed enzyme-drug interaction. Duvelisib and Robinin herbs are the best TP53 potential medications. Duvelisib, an inhibitor of phosphatidylinositol 3-kinase delta and gamma, is not tried for acute lymphocytic leukaemia in chemotherapy 48; instead, it is used to treat relapsed or refractory chronic lymphocytic leukaemia. Through a glycosidic linkage, a 6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-galactopyranosyl residue at position 3 and a 6-deoxy-alpha-L-mannopyranosyl residue at position 7 kaempherol substitute the glycosyloxyflavone known as robin. It serves as a metabolite for plants. Both a dihydroxyflavone and a glycosyloxyflavone are present.

Conclusion

In the present study virtual screening of FDA-approved drugs retrieved from the DrugBank database was carried out against the TP53 Pro72Arg (rs1042522) cancer drug target. Different computational tools were used in this study which leads to the identification of drugs against cancer. In terms of docking score, and stability, the two drugs Duvelisib and robinin herb were found as the most effective drugs among all the drugs of the DrugBank database. Overall, the two drugs Duvelisib and robinin herb revealed a strong binding affinity toward the TP53. These drugs can be helpful to treat cancer. However, to validate the results of our investigation, additional in vitro and in vivo studies are recommended.

Availability of data and materials

Data from this study will be made available upon reasonable request.

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Funding Statement

This research received no external funding.

Ethics declaration

Conflict of interest

The authors declare no conflict of interest.

Ethics Approval: Approval NO. Dir A&R AWKUM 2020/5118 was received for the current study from Abdul Wali Khan University's Institute Review Board (IRB), located in Mardan, KPK, Pakistan.

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