Experimed 2023; 13(3): 205-212

RESEARCH ARTICLE

DOI: 10.26650/experimed.1358971

Exploring PI3K Pathway Inhibitors for Acute Myeloid Leukemia: A Drug-Repurposing Approach

Cansu Ergun[1], Buse Zeren Kiremitci[1], Gizem Arslantas[1], Busenur Bozkurt[1], Gizem Ayna Duran[1], Yagmur Kiraz[1]

[1]Department of Genetics and Bioengineering, Faculty of Engineering, Izmir University of Economics, Izmir, Turkiye

ORCID ID: C.E. 0009-0004-4968-0315; B.Z.K.0009-0005-1478-0858; G.A. 0009-0008-0693-0731; B.B. 0009-0007-9154-1847; G.A.D. 0000-0002-2168-753X; Y.K. 0000-0003-3508-5617

Cite this article as: Ergun C, Kiremitci BZ, Arslantas G, Bozkurt B, Duran GA, Kiraz Y. Exploring PI3K pathway inhibitors for acute myeloid leukemia: a drug-repurposing approach. Experimed. Experimed 2023; 13(3): 205-212.

ABSTRACT

Objective: Acute myeloid leukemia (AML) is a malignant disease characterized by the uncontrolled growth, differentiation, and proliferation of immature hematopoietic cells. Patients with AML often have poor survival rates, which are associated with specific gene mutations in *FLT3, CEBPA*, and *NPM1*. The phosphatidylinositol 3-kinase (PI3K) pathway, a lipase pathway, is activated in many malignancies, including AML. Given the low survival rates in AML, this study identified candidate drugs that could inhibit the PI3K pathway, thereby offering a potential treatment for AML, by using a drug-repurposing approach.

Materials and Methods: Online bioinformatics tools were utilized to identify pathway-related genes and FDA-approved drugs. Subsequently, molecular docking was performed to determine the binding affinity values. Important genes were identified by evaluating their impact on survival and their aberrant expression in the tumor. In this study, genes such as *VAV1, GSK3B, MTOR, PDPK1, PRR5, TSC2, AKT3,* and *CREB1* were determined and docked with their potential inhibitors. Particular attention was paid to *VAV1* because there were no known potential *VAV1* inhibitors used in AML.

Results: The docking results were ranked, and the proposed gene–drug pairs were identified as tideglusib and fostamatinib for the inhibition of *GSK3B*, pimecrolimus and fostamatinib for the inhibition of *MTOR*, and fostamatinib for the inhibition of *PDPK1*. Furthermore, nebivolol, darifenacin, dihydroergotamine, libanserin and entereg were identified as potential inhibitors of *VAV1* in AML.

Conclusion: To sum up, most effective gene–drug pairs according to binding affinities were proposed as candidate inhibitor drugs for AML.

Keywords: AML, repurposing, molecular docking, survival, PI3K pathway, *VAV1*

INTRODUCTION

As a malignant disease, acute myeloid leukemia (AML) is a disorder of the hematopoietic system. Blasts of the myeloid lineage differentiate abnormally with clonal expansion. This uncontrollable proliferation led to immature blast cell accumulation and consequently to several infections such as anemia. AML is the most prevalent type of leukemia in adults, with the average age of diagnosis being 68. The genesis of AML remain largely unknown. However, stem cell analysis has provided insights into the self-renewal capabilities of hematopoietic progenitors and their potential for oncogenic transformation. These progenitors are typically dormant and rare, contributing to chemotherapy resistance and disease recurrence. In addition, some specific mutations in *ASXL1*, *TET2*, and *DNMT3A* were detected before the genesis of leukemia in hematopoietic progenitors. These mutations were considered to be primary indicators of leukemia occurrence (1).

For the diagnosis of AML, the threshold for the amount of myeloblasts in peripheral blood or bone marrow is set at 20%. The World Health Organization's 2008 classification of AML is based on oncogenes such as *FLT3, CEBPA*, and *NPM1*. These genes are of significant importance in the

Corresponding Author: Yagmur Kiraz **E-mail:** yagmur.kiraz@ieu.edu.tr
Submitted: 19.09.2023 **Revision Requested:** 09.10.2023 **Last Revision Received:** 17.10.2023 **Accepted:** 01.11.2023

prognosis of AML. Approximately 50% of AML cases exhibit an *NPM1* mutation. Additionally, 25–45% of cases possess *FLT3* mutations, and 5–10% of patients have *CEBPA* mutations (2). Other genetic abnormalities, such as mutations in *RUNX*, *TP53*, and *IDH1*, are also detected in AML cases (3). AML is cured using conventional therapy, mutation-specific targeted therapy, immunotherapy, apoptotic pathway targeted therapy, checkpoint inhibitors, vaccines, checkpoint inhibitors, and cellular therapy (4).

The PI3K pathway contributes to several cellular mechanisms such as metabolism, survival, transcription and translation, proliferation, organization of the cytoskeleton, and growth (5, 6). The PI3K signaling pathway is a member of the heterodimeric lipid kinase family. PI3K proteins are divided into three groups of isomers 1, 2, and 3. Class 1A proteins of the PI3K family are activated by tyrosine kinases, while the activation of class 1B proteins is maintained by the G protein receptor. Upon activation by an external or internal messenger, PI3K triggers various mechanisms. In contrast, the phosphatase and tensin homolog (PTEN) acts as a tumor suppressor gene and a negative regulator of the pathway (5). This pathway is overactivated in many types of cancer. There are two specific activation mechanisms of the pathway: tyrosine kinase activation and mutations in the pathway elements. Moreover, the functional loss of the *PTEN* gene promotes the stimulation of the PI3K pathway (6).

AML patients generally exhibit an activated pattern in the PI3K pathway. This activation decreases the survival rate of the patients. PI3K plays a crucial role in hematopoietic cell functions, including survival, differentiation, and proliferation. Additionally, the *FLT3* gene, which is commonly mutated in AML cases, stimulates pathway activation (7).

Conventional chemotherapy serves as one of the treatment options for AML, with daunorubicin and cytarabine being commonly used as chemotherapy agents (8). In addition to conventional therapy, targeted therapy presents a promising alternative for patients. Given that the *FLT3* gene is frequently mutated in AML patients, midostaurin is employed as an *FLT3* inhibitor. Furthermore, enasidenib and ivosidenib are used to inhibit mutated *IDH1*, while decitabine and venetoclax are used to inhibit *DNMT3A* and *BCL2*, respectively (9). In addition to these currently used therapies, specific mutated protein targeted therapies have been developed owing to a better understanding of the genomic complexity of AML. Menin inhibitors that target *KMT2Ar* or *NPM1*, *TP53*-targeted drugs, and apoptotic inhibitors that target MCL1 and PDL-1 targeted inhibitors as immune checkpoint inhibitors were developed to effectively treat AML patients according to their genomic circumstances (10). Development, preclinical studies, and clinical trials are the steps of drug development for a specific indication. Indeed, the process of drug development is highly complex and requires significant investment and time. To overcome these challenges, drug repurposing is often employed. This involves using drugs to treat diseases that are different from their original intended use. Aspirin and sildenafil are well-known examples of repurposed drugs. Sildenafil, for instance, was originally developed for heart diseases, but it was later discovered to be effective for treating erectile dysfunction. Likewise, aspirin was originally an anti-inflammatory drug that was described as a preventative drug for several cancers, such as gastric, colorectal, and ovarian cancers (11).

Inhibition of the PI3K pathway in AML patients has a novel therapeutic significance in increasing the survival rate of patients and the success of the therapy. Our study identifies FDA-approved inhibitory drugs for pathway inhibition through a repurposing approach.

MATERIALS AND METHODS

Identification of PI3K Pathway-related Genes in AML

The KEGG and DAVID databases were utilized to identify genes related to the PI3K pathway (12, 13). Genes obtained from these databases were analyzed in terms of their relationship with AML by using CTD databases (14).

Gene Expression and Survival Plot Analysis

The genes were analyzed in order to compare their expression levels between AML patients and normal samples. This analysis was conducted using the GEPIA web tool. The most differentially expressed genes were also analyzed to identify their effect on survival rates in patients with AML (15).

Determination of Inhibitory Drugs

The inhibitors targeting the identified genes were determined using the DrugBank database, applying specific filters: those not used in any clinical trial for AML treatment and FDA approved (16). The ZINC15 database is known to comprise over millions of compounds; therefore, to achieve a comprehensive analysis to identify inhibitor drugs for repurposing, the ZINC15 database was used with the filters of "named," "FDA approved," and "for sale" (17). We have excluded drugs that are still in clinical trials or lack validation from further studies. This decision was made to focus our work exclusively on commercially available and FDA-approved drugs.

Molecular Docking

The 3D structures of candidate target proteins were obtained from the PDB and/or AlphaFold databases (18, 19). In addition, ligand structures were sourced from the PubChem and Zinc15 databases for subsequent docking analysis (17, 20).

The structures of *AKT3*, *PDPK1*, *MTOR*, *GSK3A*, *TSC2*, and *CREB1* genes were obtained from the AlphaFold database (19). The binding sites of these structures were identified based on literature and Biovia Discovery Studio (21). For *AKT3*, the binding site was determined at coordinates x = −15.687, y = 5.811, and z = 16.164 (21). The PIF region of the PDPK1 gene was designated as the active site of the structure (22). Additionally, the active region of the *MTOR* gene was identified between the coordinates x = −8.123, y = 26.991, z = 36.301. Similarly, for the *GSK3A* gene, the active region was defined as x = 24.996, y = 24.926, z = 27.613. For *CREB1* gene, x =5.5, y = 5.5, z =−10

was the coordinate of the binding region, and the *TSC2* gene binds actively to the ligand between x = 10, y = 1, and z = 0.2 coordinates (21).

The PDB database was employed to identify the structures of *NR4A1*, *GSK3B*, and *VAV1* genes. The 3D structure with PDB code "2QW4" was associated with *NR4A1*. This structure, recognized as the ligand binding domain of the gene, was utilized in its entirety for docking analysis. For the *GSK3B* gene, the structure with code "5K5N" was utilized, and the ligand binding region was specified with coordinates x = 24.996, y = 24.926, z = 27.613 (18, 23). 3D structure of the *VAV1* gene was detected as "6NFA" code from the PDB database (18). However, binding regions of the *VAV1* structure could not be found in the literature. Therefore, the structure was analyzed by using PyMol with the "center of mass" command. The mass center of the structure was between x = –0.791, y = 8.502, z = –24.333 coordinates and this region was determined as a binding region of the *VAV1* gene (24). Autodock Vina was used to perform docking analysis (25).

Toxicity Analysis

Eleven ligands (Raloxifene, Accolate, Nebivolol, Darifenacin, Flibanserin, Indinavir, Glipizide, Dihydroergotamine, Entereg (Alvimopan), Suvorexant, and Ergotamine) successfully docked with *VAV1*, exhibiting high docking scores. These ligands were subjected to analysis using ProTox-II, a tool for predicting the toxicity of chemicals, to unveil their toxicity parameters (26).

RESULTS

Identified Genes were PI3K Related, Overexpressed in AML, and Related to Poor Prognosis in AML

Using the KEGG and DAVID databases, primary genes of the PI3K pathway were detected. For further analysis, the CTD database was used, and 90 genes related to the AML and PI3K pathway were detected (12, 13, 14). The analysis of these 90 genes was conducted using the GEPIA database to assess their impact on patient survival and expression level increases in tumor samples (15). Among them, 14 genes emerged as significant, demonstrating both high gene expression levels and a hazardous status in terms of patient survival. The identified genes include *AKT3, CREB1, GAB1, GSK3A, GSK3B, HGF, MTOR, NR4A1, NRG4, PDPK1, PIK3AP1, PRR5, TSC2,* and *VAV1*, as detailed in Table 1.

Potential Inhibitor Drugs Identified for Selected Genes

In structure based virtual screening, predicted ligand classification and evaluation play crucial roles in several courses of computational drug design. Chemical library screening, characterization, and prediction of potential targets for combination of small molecules are included in this process. To implement this process, the Drug Bank and ZINC15 database were screened by focusing on nine specific candidate genes for the study to identify the targeted drugs associated with each gene (16, 17). Consequently, twenty one drugs for *AKT3*, four for *CREB1*, four for *GSKA*, ten for *NR4A1*, five for *HGF*, one for *GSK3B*, three for *TSC2*, four for *MTOR*, and thirty four for *PDPK1* were recorded. No drugs targeting the *GAB1*, *PRR5*, *NRG4A*, and *PI3AP1* genes were identified. However, one drug was found to inhibit the action of *VAV1*. Notably, the *HGF* gene was excluded from the study due to its reverse survival plot compared to hazardous genes (15).

Table 1: PI3K-related genes obtained from the KEGG, DAVID, and CTD databases and subsequently analyzed using the GEPIA tool.

GENE ID	NAME
AKT3	AKT serine/threonine kinase 3
CREB1	Camp responsive element binding protein
GAB1	GBR2 associated binding protein
GSK3A	Glycogen synthase kinase 3 alpha
GSK3B	Glycogen synthase kinase 3 beta
HGF	Hepatocyte growth factor
MTOR	Mechanistic target of rapamycin kinase
NR4A1	Nuclear receptor subfamily 4 group A member
NRG4	Neuregulin 4
PDPK1	3-phosphoinositide dependent protein kinase 1
PIK3AP1	Phosphoinositide-3-kinase adaptor protein
PRR5	Proline rich 5
TSC2	TSC complex subunit 2
VAV1	Guanine nucleotide exchange factor 1

FDA-approved Drugs Paired with Selected Genes

To identify potential new therapeutic agents, we conducted a drug screening process. We focused on drug candidates that had not been previously studied in patients with AML but were FDA approved for other indications. During the screening process, certain drugs were eliminated for each gene, resulting in the following recorded gene–drug pairs: *AKT3*: fostamatinib, anastrozole, and fulvestrant, *GSK3A*: fostamatinib, *TSC2*: cannabidiol, *PDPK1*: fostamatinib, *CREB1*: citalopram, *NR4A1*: acetylcysteine, *GSK3B*: tideglusib, *MTOR*: pimecrolimus and fostamatinib. It is important to highlight that epoetin alpha was previously proposed for the *VAV1* gene. Nevertheless, this inhibitor drug did not meet the criteria set by our filters.

Binding Affinities of Drugs Ranked as per Threshold

Docking analysis was conducted using these pairs, and the pairs were ranked based on the docking results to identify the strongest inhibitory effect on the pathway. The results were sorted according to the binding affinities of the ligands to the genes. For *AKT3*, the binding affinities of the drugs were –4.9 kcal/mol, –6.2 kcal/mol, and –6.9 kcal/mol for fostamatinib, anastrozole, and fulvestrant, respectively. Fostamatinib exhibited an affinity of –8.2 kcal/mol for *PDPK1*. *MTOR* was

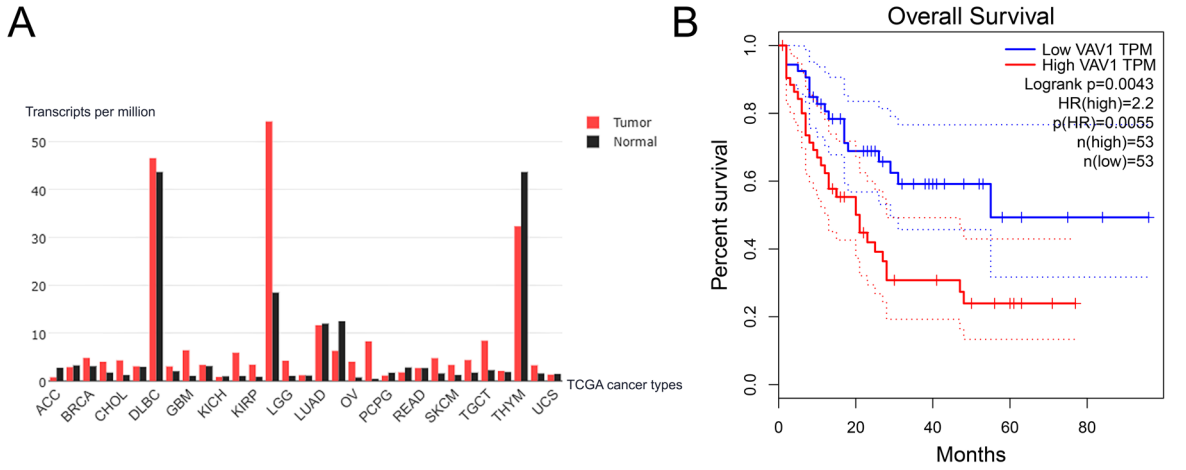

Figure 1. *VAV1* expression and survival plot in patients with acute myeloid leukemia, analyzed using GEPIA. A) The expression plot of *VAV1*; the black bar represents normal expression levels, while the red bar represents tumor expression levels. B) The survival plot of *VAV1* with a p-value of 0.0043 and a hazard ratio of 2.2; the red line indicates high expression levels, while the blue line indicates low expression levels.

paired with two inhibitors, and pimecrolimus gave a binding affinity of –19 kcal/mol to the gene. This higher affinity could not be recorded with any of the gene–drug pairs. This high binding affinity, assumed to be caused by pimecrolimus, is a well-known MTOR inhibitor. Furthermore, fostamatinib and the *MTOR* pair bind with an affinity of –8.4 kcal/mol. The docking results of acetylcysteine and *NR4A1* were –4.5 kcal/mol. This result was found to be less significant when compared with other pairs. Tideglusib gave an affinity of –8.3 kcal/mol with *GSK3B*, and the binding affinity of fostamatinib was recorded as–9 kcal/mol. The *TSC2* and cannabidiol ligand pair gave the best affinity result as –5.5 kcal/mol. Fostamatinib binds *GSK3A* with a binding affinity of –7.4 kcal/mol, and the *CREB1*–citalopram pair showed an affinity of –4.2 kcal/mol.

The binding affinity results were sorted based on whether they were below or above the threshold of –8.0 kcal/mol, considering all recorded results. Pairs with binding affinity below the specified threshold were documented as effective inhibitory pairs (Table 2).

Table 2: Binding affinity results for *PDPK1*, *MTOR*, and *GSK3B* genes and their paired drugs that fall below the threshold of –8.0 kcal/mol.

GENE	DRUG	BINDING AFFINITY (kcal/mol)
PDPK1	Fostamatinib	–8.2
MTOR	Pimecrolimus	–19.0
	Fostamatinib	–8.4
GSK3B	Tideglusib	–8.3
	Fostamatinib	–9.0

Drug Identification of *VAV1* and Docking Analysis of Candidate Drugs

Because there were not proper inhibitors for *VAV1*, although the gene is novel and hazardous for AML patients (Figure 1), drugs were screened by using the ZINC 15 database for the inhibition of *VAV1* (17). A total of 1,400 candidate drugs were retrieved from the database. Drugs with binding affinities above –9.0 kcal/mol, representing the best pairs, were subjected to docking. The analyzed drugs were further assessed for their clinical trial status in AML and their impact on specific organs. The drugs that remained in consideration, namely suvorexant, nebivolol, darifenacin, ergotamine, accolate, raloxifene, dihydroergotamine, glipizide, flibanserin, indinavir, entered with binding affinities above –9.0 kcal/mol (Figure 2).

VAV1-paired Cytotoxic Drugs were Eliminated

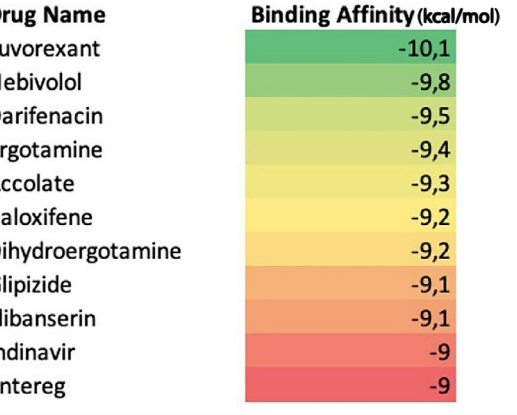

Figure 2. Binding affinities that fall below the threshold of –9.0, as determined by the molecular docking analysis results for *VAV1*.

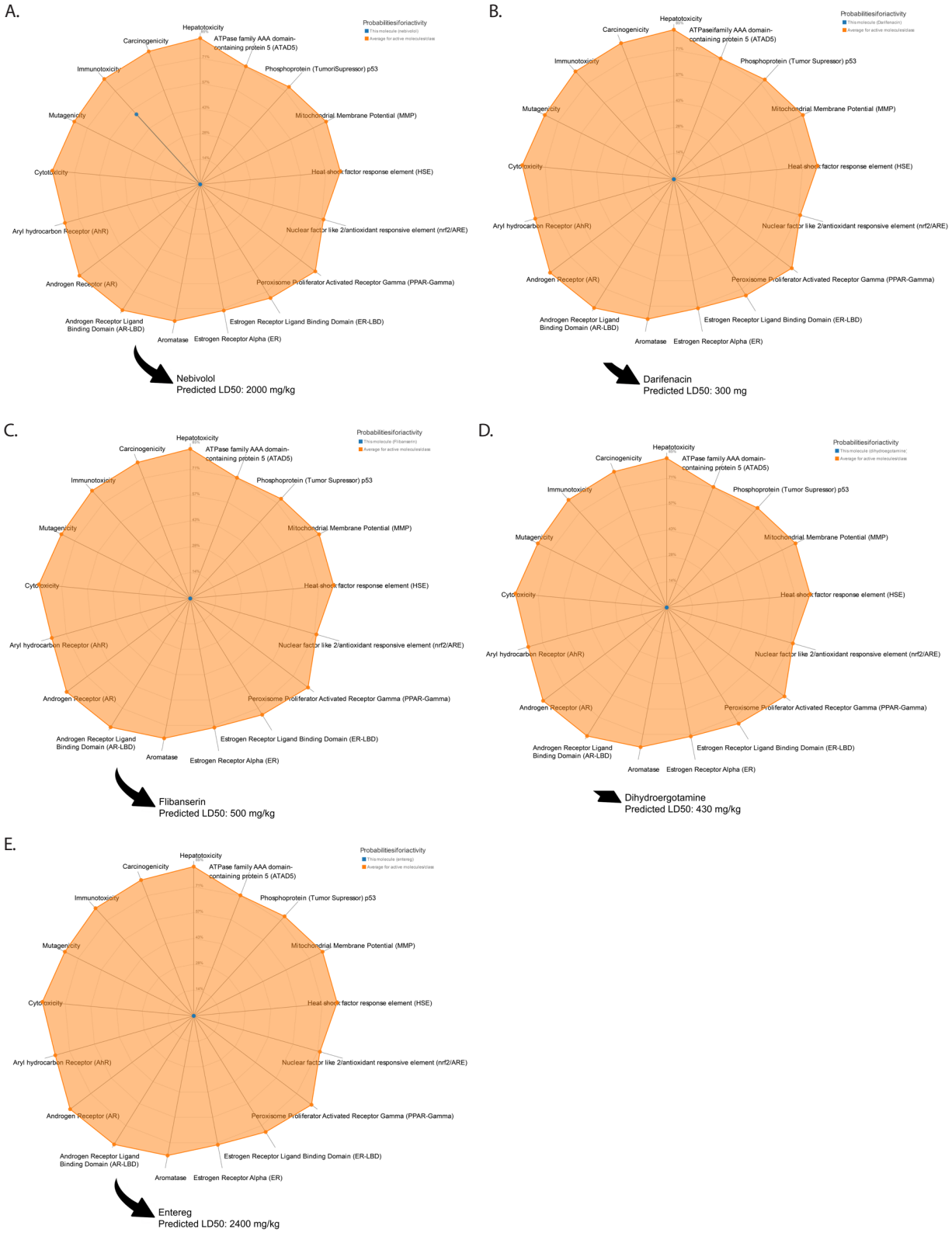

Figure 3. Toxicity analysis of drugs paired with *VAV1* and possessing high binding affinity, as analyzed using Protox-II. A) Nevivolol with an LD50 of 2000 mg/kg. B) Darifenacin with an LD50 of 300 mg/kg. C) Flibanserin with an LD50 of 500 mg/kg. D) Dihydroergotamine with an LD50 of 430 mg/kg. E) Entereg with an LD50 of 2400 mg/kg.

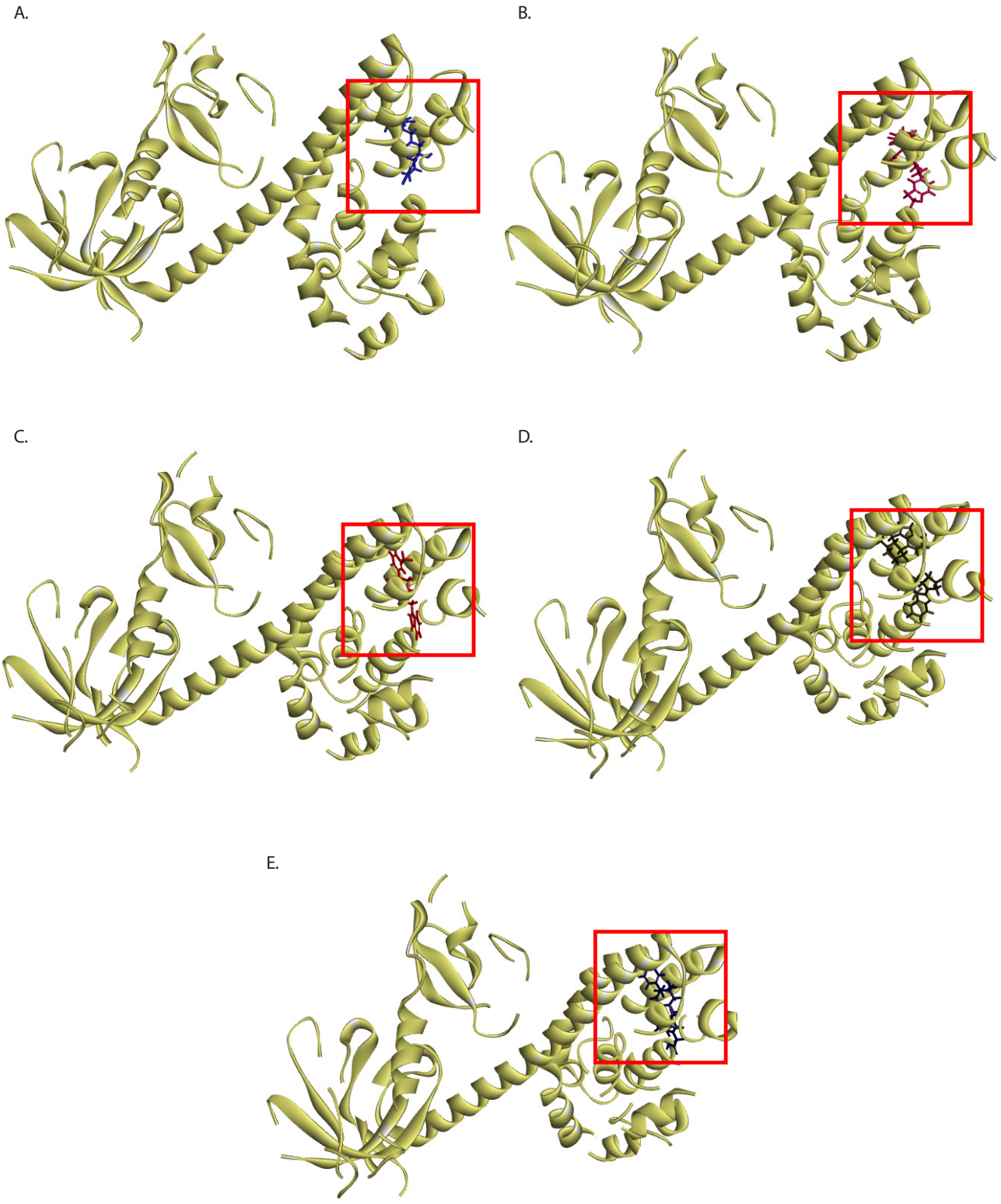

Figure 4: Molecular docking model of proposed drugs paired with *VAV1*, as visualized using Biovia Discovery Studio. The red squares indicate the ligand. A) Nebivolol, B) Darifenacin, C) Flibanserin, D) Dihydroergotamine, E) Entereg.

Due to the fact that the initially paired candidate drugs for the *VAV1* gene are not inherently inhibitors of the gene, concerns were raised regarding the toxicity status of these drugs. To address this, a toxicity analysis of the selected drugs was conducted using the Pro-tox-ii database (26). The toxicity model provided active and inactive predictions, along with LD50 values (Figure 3), where values of 2500 mg/kg and above were considered non-toxic. Subsequently, drugs were excluded based on their clinical trial status in AML and their lack of antipsychotic properties. The drugs that remained in consideration, namely nebivolol, darifenacin, dihydroergotamine, flibanserin, glipizide, and entereg, were confirmed as inhibitors of *VAV1* (Figure 4).

DISCUSSION

AML is a highly lethal cancer type with very low survival rates. The survival of patients with AML is significantly influenced by the activation of various signaling pathways. One such critical pathway is the PI3K pathway, which is known to be activated in numerous cancer types, including AML. To counteract this activation, both dual and single inhibitors are employed to inhibit PI3K activity in patients (27). In our study, the initial step involved identifying genes associated with the PI3K pathway using pathway analysis tools. Subsequently, these related genes underwent analysis to assess their expression levels and impact on patient survival. We then identified potential inhibitor drugs that were both FDA approved and novel in the context of AML treatment from online databases. The interaction between potential drugs and gene structures was further explored using molecular docking techniques to determine their binding affinities. According to the docking results, thresholds were determined for the *VAV1* gene as −9.0 and −8.0 for other genes of interest, and gene–drug pairs were ranked and potential pairs were identified. The best gene–drug pairs with the highest binding affinities *VAV1* were proposed to be the *VAV1*: nebivolol, darifenacin, dihydroergotamine, flibanserin, and entereg; *GSK3B*: tideglusib and fostamatinib; *MTOR:* pimecrolimus and fostamatinib; and *PDPK1*: fostamatinib.

We cite similar studies from the literature that propose the dual inhibition of PI3K and AKT pathways for AML treatment. Specifically, a compound C16, was suggested as an inhibitor of both pathways based on molecular docking results involving PI3K and AKT proteins, specifically PI3KCG, PI3KCD, and AKT (26-28).

Furthermore, a molecular docking approach was used to determine inhibitor drugs for AML. RNA-seq data were obtained and genes were analyzed to determine differentially expressed genes. In addition, enrichment and network analysis were performed. Following these analyses, the *CFD* and *ALDH1A1* genes were identified as prognostic target genes in AML. Molecular docking was then conducted to assess the inhibitory effects of paired drugs on these genes. The structures of the biomarkers were acquired from the PDB, and FDA-approved drugs were searched for docking analysis. Enasidenib and *ALDH1A1*, as well as gilteritinib and *CFD*, exhibited the best binding affinities and were proposed as inhibitor pairs for AML treatment (29).

Our study is guided and motivated by the findings from similar studies, which encompass analyses of FDA-approved existing drugs for repurposing candidate drugs, molecular docking analyses, and endeavors to propose novel drug–gene pairs. Most importantly, investigations to identify the most effective and novel inhibitory drugs for target prognostic genes.

Moreover, identification of *VAV1* as a potential target for AML treatment was the most significant outcome of our study because of its novelty and effect on the survival of patients with AML. In a very similar study, the *VAV* gene family was previously shown to be associated with a poor prognosis of AML. This study used several databases to identify the effect of the *VAV* gene family on the prognosis of AML. Additionally, a gene network analysis was conducted. Following computational findings, *VAV1* was identified as being over-expressed in KG-1 and MV4-11 AML cell lines. Subsequently, the GEPIA dataset was utilized to assess the impact of *VAV1* on survival. The survival plot for *VAV1* revealed a diminished profile as the gene's expression increased (30). While our study primarily comprised computational findings, the results from Mu et al. served as a guide for further analysis of *VAV1* activity in AML disease (30). The consistency in identifying the adverse prognostic effect of *VAV1* underscores the novelty and targetability of this gene

CONCLUSION

In summary, our objective was to identify inhibitor drug candidates for the treatment of AML by targeting the PI3K pathway, utilizing FDA-approved existent drugs originally developed for specific indications other than AML. Through various database and molecular docking analyses, we proposed the most effective gene–drug pairs as the most suitable candidates. These pairs include *GSK3B* with tideglusib and fostamatinib, *MTOR* with pimecrulimus and fostamatinib, and *PDPK1* with fostamatinib. Additionally, we identified *VAV1* as a novel target and therapeutic candidate for pathway inhibition, suggesting its combination with nebivolol, darifenacin, dihydroergotamine, flibanserin, glipizide, and entereg. Moreover, *VAV1* is proposed for further analysis and investigation due to its significance for AML.

Ethics Committee Approval: A publicly available dataset of AML patients from the GEPIA database was used. Ethics committee approval was excluded in this study because online bioinformatics tools are open sources and freely used in all research.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Y.K., Data Acquisition- C.E., B.Z.K., G.A., B.B. Data Analysis/Interpretation- G.A.D., Y.K.; Drafting Manuscript- C.E., G.A.D., Y.K., B.Z.K., G.A., B.B.; Critical Revision of Manuscript- G.A.D., Y.K.; Final Approval and Accountability- C.E., G.A.D., Y.K., B.Z.K., G.A., B.B.

Conflict of Interest: All authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. Lancet 2018; 392(10147): 593–606.
2. Hasserjian RP. Acute myeloid leukemia: advances in diagnosis and classification. Int J Lab Hematol 2013; 35(3): 358–66.
3. Kayser S, Levis MJ. Clinical implications of molecular markers in acute myeloid leukemia. Eur J Haematol 2019; 102(1): 20-35.
4. Short NJ, Konopleva M, Kadia TM, Borthakur G, Ravandi F, DiNardo CD, et al. Advances in the treatment of acute myeloid leukemia: new drugs and new challenges. Cancer Discov 2020; 10(4): 506–25.
5. Jiang N, Dai Q, Su X, Fu J, Feng X, Peng J. Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. Mol Biol Rep 2020; 47(6): 4587–629.
6. The relation between PI3K/AKT signaling pathway and cancer. Gene 2019; 698: 120–8.
7. Nepstad I, Hatfield KJ, Grønningsæter IS, Reikvam H. The PI3K-Akt-mTOR signaling pathway in human acute myeloid leukemia (AML) Cells. Int J Mol Sci 2020; 21(8): 2907.
8. Kantarjian HM, Short NJ, Fathi AT, Marcucci G, Ravandi F, Tallman M, et al. Acute myeloid leukemia: historical perspective and progress in research and therapy over 5 decades [Internet]. Vol. 21, Clinical Lymphoma Myeloma and Leukemia. Elsevier BV; 2021. p. 580–97.
9. Fleischmann M, Schnetzke U, Hochhaus A, Scholl S. Management of acute myeloid leukemia: current treatment options and future perspectives. Cancers 2021; 13(22): 5722.
10. Totiger TM, Ghoshal A, Zabroski J, Sondhi A, Bucha S, Jahn J, et al. Targeted therapy development in acute myeloid leukemia. Biomedicines 2023; 11(2): 641.
11. Turabi KS, Deshmukh A, Paul S, Swami D, Siddiqui S, Kumar U, et al. Drug repurposing—an emerging strategy in cancer therapeutics. Naunyn Schmiedebergs Arch Pharmacol 2022; 395(10): 1139–58.
12. KEGG pathway Database [Internet]. [cited 2023 Aug 25]. Available from: https://www.genome.jp/kegg/pathway.html
13. DAVID Functional Annotation Bioinformatics Microarray Analysis [Internet]. [cited 2023 Aug 25]. Available from: https://david.ncifcrf.gov/home.jsp
14. The Comparative Toxicogenomics Database [Internet]. [cited 2023 Aug 25]. Available from: https://ctdbase.org/
15. GEPIA (Gene Expression Profiling Interactive Analysis) [Internet]. [cited 2023 Aug 25]. Available from: http://gepia.cancer-pku.cn/
16. DrugBank Online [Internet]. [cited 2023 Aug 25]. Available from: https://go.drugbank.com/
17. ZINC [Internet]. [cited 2023 Aug 25]. Available from: https://zinc15.docking.org/
18. Bank RPD. RCSB PDB: Homepage [Internet]. [cited 2023 Aug 25]. Available from: https://www.rcsb.org/
19. Database APS. AlphaFold Protein Structure Database [Internet]. [cited 2023 Aug 25]. Available from: https://alphafold.ebi.ac.uk/
20. PubChem. PubChem [Internet]. [cited 2023 Aug 25]. Available from: https://pubchem.ncbi.nlm.nih.gov/
21. BIOVIA Discovery Studio - BIOVIA - Dassault Systèmes® [Internet]. [cited 2023 Aug 25]. Available from: https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/
22. Collins BJ, Deak M, Arthur JSC, Armit LJ, Alessi DR. In vivo role of the PIF-binding docking site of PDK1 defined by knock-in mutation. EMBO J 2003; 22(16): 4202–11.
23. Ogunleye AJ, Olanrewaju AJ, Arowosegbe M, Omotuyi OI. Molecular docking based screening analysis of GSK3B. Bioinformation 2019; 15(3): 201-8.
24. PyMOL [Internet]. [cited 2023 Aug 25]. Available from: https://pymol.org/2/
25. Welcome to the PyRx Website [Internet]. [cited 2023 Aug 25]. Available from: https://pyrx.sourceforge.io/
26. ProTox-II - Prediction of TOXicity of chemicals [Internet]. [cited 2023 Aug 25]. Available from: https://tox-new.charite.de/protox_II/
27. Rodrigues ACBDC, Costa RGA, Silva SLR, Dias IRSB, Dias RB, Bezerra DP. Cell signaling pathways as molecular targets to eliminate AML stem cells. Crit Rev Oncol Hematol 2021; 160: 103277.
28. Abohassan M, Alshahrani M, Alshahrani MY, Rajagopalan P. Insilco and Invitro approaches identify novel dual PI3K/AKT pathway inhibitors to control acute myeloid leukemia cell proliferations. Med Oncol 2022; 39(12): 1–10.
29. Alom MM, Faruqe MO, Molla MKI, Rahman MM. Exploring prognostic biomarkers of acute myeloid leukemia to determine its most effective drugs from the FDA-approved list through molecular docking and dynamic simulation. Biomed Res Int 2023; 2023: 1946703.
30. Mu D, Long S, Guo L, Liu W. High Expression of VAV gene family predicts poor prognosis of acute myeloid leukemia. Technol Cancer Res Treat 2021: 20: 15330338211065877.