

Original Research

Network Pharmacology and Molecular Docking Reveal Potential Mechanisms of *Artemisia herba-alba* Against Acute Myeloid Leukemia

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Academic Editor: Graham Pawelec

Submitted: 10 March 2026 Revised: 20 July 2026 Accepted: 9 September 2026 Published: 26 October 2026

Abstract

Background: *Artemisia herba-alba* is a phytochemically diverse medicinal plant known for its high concentrations of sesquiterpene lactones and flavonoids with purported anticancer properties. Despite its potential, the specific molecular mechanisms through which its individual constituents modulate acute myeloid leukemia (AML) are not yet fully understood from a compound-centered, multi-target perspective. **Methods:** Phytocompounds reported in *A. herba-alba* were collected and screened for predicted drug-likeness, pharmacokinetic viability, and safety profiles. Putative human targets were predicted using chemogenomic platforms and intersected with AML-associated genes from public databases and transcriptomic datasets. A protein-protein interaction network was constructed to identify central hub targets, which were further analyzed through pathway enrichment and molecular docking to estimate predicted binding affinity and binding poses. **Results:** Fourteen compounds met the criteria for favorable physicochemical and safety profiles and were predicted to target 34 AML-related proteins. Network-based analysis identified potassium channels, phospholipase A2 (PLA2), cytochrome P450 monooxygenases (CYPs), and arachidonate-5-lipoxygenase (ALOX5) as key network hubs. These hubs are primarily associated with lipid metabolism, immune signaling, and xenobiotic pathways. Molecular docking further predicted favorable binding interactions of herbolide B, acacetin, and moxartenolide with multiple hub proteins, supporting their prioritization as potential multi-target compounds for further investigation. **Conclusion:** This chemistry-driven network analysis identifies *A. herba-alba* phytocompounds with favorable predicted drug-like properties and potential interactions with AML-relevant molecular targets. These findings provide computationally derived hypotheses regarding possible pathways and compound-target relationships that may contribute to the biological effects of these phytocompounds. Experimental studies are required to determine whether the predicted interactions translate into target modulation and therapeutic activity in AML.

Keywords: *Artemisia herba-alba*; network pharmacology; acute myeloid leukemia; phytocompounds; drug-likeness; pharmacokinetics

1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematopoietic malignancy characterized by the clonal expansion of immature myeloid cells and a profound blockade in the differentiation of hematopoietic stem and progenitor cells. This disruption of normal hematopoiesis results in bone marrow failure and severe clinical complications. AML typically arises from the malignant transformation of progenitor cells; while clonal hematopoiesis can be a feature of normal aging, the accumulation of specific genetic and epigenetic alterations facilitates clonal dominance. Over time, these aberrant clones may acquire secondary mutations that drive disease progression and culminate in overt AML [1].

Clinically, AML presents with systemic symptoms including weakness, dyspnea, ecchymosis, and hemorrhage [2]. Primarily an adult-onset disease, its pathogenesis is closely linked to age-associated mutational ac-

cumulation [3]. The hallmark of the disease is the disproportionate accumulation of immature white blood cells within the bone marrow and peripheral blood circulation [4]. These leukemic blasts exhibit hallmark malignant behaviors, including uncontrolled proliferation driven by abnormal growth signaling, resistance to programmed cell death, impaired differentiation, genomic instability, and metastatic potential [5].

The management of AML is complicated by its vast molecular heterogeneity. The disease is categorized into various subtypes based on distinct cytogenetic and molecular features, which influences everything from initial diagnosis to therapeutic selection [6]. Pathogenesis involves significant genetic alterations across multiple functional gene categories, including tumor suppressors, splicing factors, signaling molecules, DNA methylation regulators, chromatin modifiers, and the cohesin complex [7].

Globally, the incidence of AML is rising, with over 351,965 cases reported as early as 2012 [8]. While the



estimated prevalence in Africa is approximately 1%, it is expected to experience the highest increase in the coming decade. In Nigeria, AML accounts for 19%–24% of hospital-managed leukemias and is associated with the lowest survival rate among all leukemia types [8]. Furthermore, hospital-based studies report that hematological malignancies account for approximately 17.4%–18.0% of all cancers in Nigeria [9].

Despite advancements in AML treatment, significant barriers to effective management persist. These include high disease heterogeneity, limited financial access to approved medications, and disparities in diagnostic infrastructure [8,9]. Many current therapies are further limited by the emergence of drug resistance or dose-limiting toxicities [7]. Therefore, there is an urgent need for safe, multi-target therapeutic candidates capable of addressing the complex, multifactorial mechanisms underlying AML progression.

The present study systematically investigates the anti-leukemic potential of *Artemisia herba-alba* (white wormwood) using an integrated network pharmacology framework. Bioactive phytochemicals were screened based on their drug-likeness, pharmacokinetic properties, and predicted human target profiles. Common targets shared between *A. herba-alba* bioactives and proteins implicated in acute myeloid leukemia (AML) were identified and further evaluated by molecular docking to assess the most promising compound-target interactions. To our knowledge, this is the first study to integrate comprehensive phytochemical curation, AML transcriptomic data, multi-database target prediction, network pharmacology, and molecular docking into a unified workflow for the systematic evaluation of the anti-leukemic potential of *A. herba-alba*.

2. Methods

The methodology employed in this study is illustrated in Fig. 1.

2.1 Plant Selection and Bioactive Compound Screening

Medicinal plants with reported anticancer activity were identified using the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, <https://tcmsp-e.com/tcmssp.php>) [10] and the anti-cancer herbs database of systems pharmacology (CancerHSP) [11]. Search query keywords included “antitumor”, “anticancer”, “anti-acute myeloid leukemia”, “anti-neoplastic”, “anti-proliferative”, “pro-apoptotic”. *Artemisia herba-alba* was selected for this study due to its high reported bioactivity scores against various cancer cell lines. Phytochemical constituents of *A. herba-alba* were collated from the Phytochemical Interaction Database (PCIDB, <https://www.genome.jp/db/p/cidb>) and supplemented by systematic literature mining via PubMed (Supplementary Table 1). The Plant List database was used to verify synonyms of white wormwood to ensure comprehensive coverage. The resulting compound library was screened for drug-likeness and pharma-

cokinetic properties according to established quantitative criteria [12,13]. The integrated prioritization strategy used to identify the most promising phytochemicals for downstream analyses is summarized in Supplementary Table 2.

2.2 Identification of AML and Compound Targets

AML-associated targets were retrieved from multiple complementary databases - the TCMSP database (<https://tcmsp-e.com/tcmssp.php>) [10], SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) [14], Comparative Toxicogenomics Database (CTD; <https://ctdbase.org/?jsessionid=84E0B5D0353A4B9A77545215380F0CA7>) [15], PharmMapper (<http://www.lilab-ecust.cn/pharmmapper/>) [16], Epi-trans (<https://ips2.u-psud.fr/en/platforms/epitrans-epigenomic-translational-biology.html>) [17], and the Open Targets Platform [18] – to ensure comprehensive coverage. Additionally, transcriptomic datasets for *Homo sapiens* (GSE12417, GSE9476, GSE1729, and GSE425) were obtained from the NCBI Gene Expression Omnibus (GEO) (<https://www.ncbi.nlm.nih.gov/gds/>). Differentially expressed genes (DEGs) in AML versus healthy controls were identified using an absolute $\log_2$ FoldChange ≥ 2 and a p -value ≤ 0.005 .

To predict compound-specific targets, canonical Simplified Molecular Input Line Entry Specification (SMILES) and two-dimensional (2D) structures (mol2) were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). These data were processed using the SuperPred web server [19,20], SwissTargetPrediction [14], and PharmMapper [16]. Overlapping targets between AML-associated genes and compound-predicted proteins were identified and visualized using a Venn diagram tool (<https://bioinformatics.psb.ugent.be/webtools/Venn/>).

2.3 Protein-Protein Interaction Network

The intersecting targets were analyzed using the STRING database (<https://string-db.org/>) to evaluate protein-protein associations in *Homo sapiens* with a medium confidence threshold (≥ 0.4). The interaction data were imported into Cytoscape (v3.10.3) (<https://cytoscape.org/>) for topological analysis. The CytoHubba plugin was employed to identify the top ten “hub” proteins based on degree centrality [21]. The final hub interaction network was visualized using yFiles layout algorithms.

2.4 Functional Enrichment and Pathway Analysis

To elucidate the biological significance of the hub targets, Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted. These analyses were performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID; <https://davidbioinformatics.nih.gov/>) and ShinyGo ([2](http://bioinformatics.s</p>
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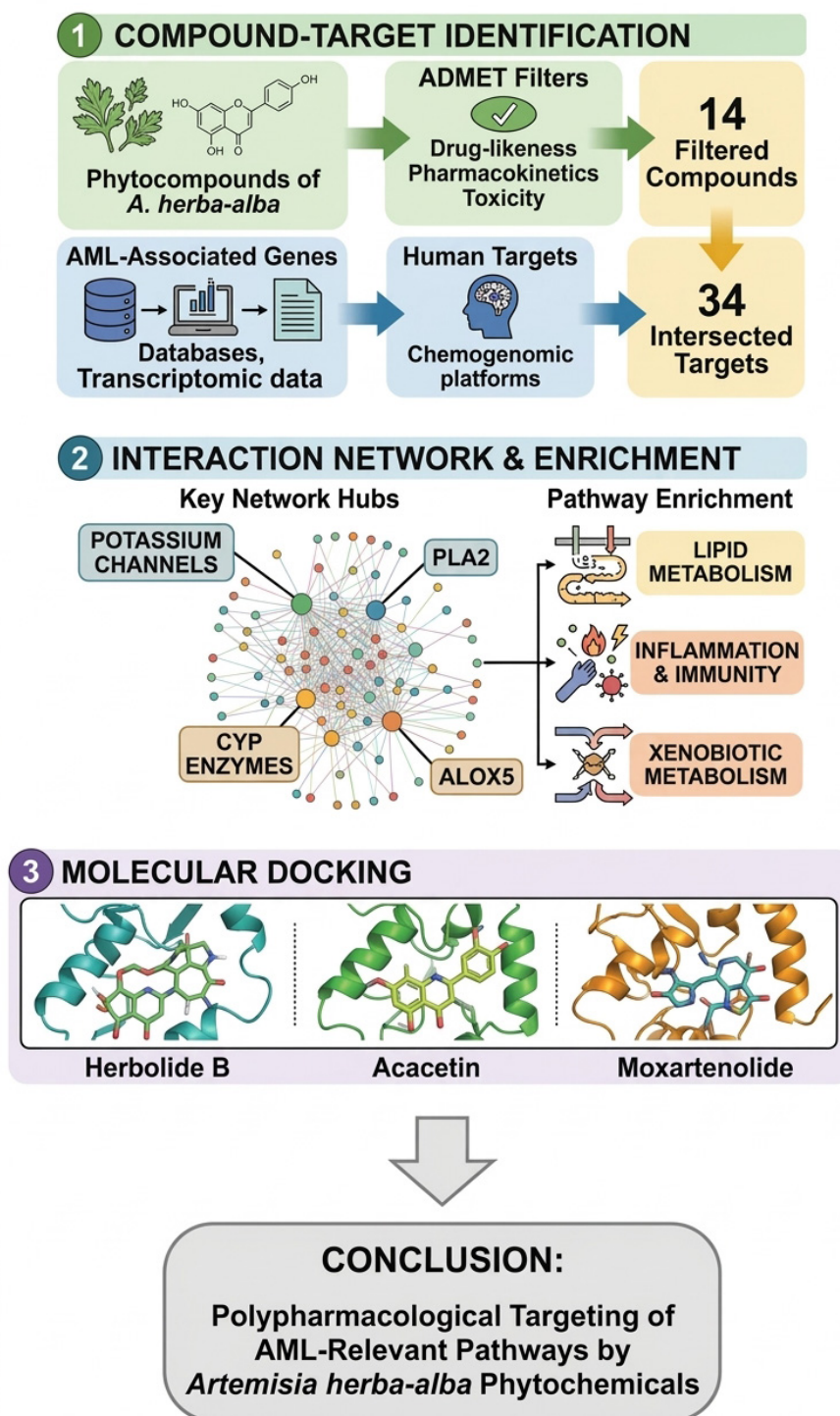


Fig. 1. Graphical overview of the study workflow. PLA2, phospholipase A2; CYPs, cytochrome P450 monooxygenases; ALOX5, arachidonate-5-lipoxygenase. The figure was created using Microsoft PowerPoint and the publicly accessible GIMP (GNU Image Manipulation Program).

dstate.edu/go/) to identify significantly enriched biological processes, molecular functions, cellular components, and signaling pathways.

2.5 Molecular Docking Simulations

Molecular docking was performed using AutoDock Vina (version 1.1.2; <https://vina.scripps.edu/>) to estimate binding affinities between the prioritized target proteins and selected white wormwood bioactive compounds. The

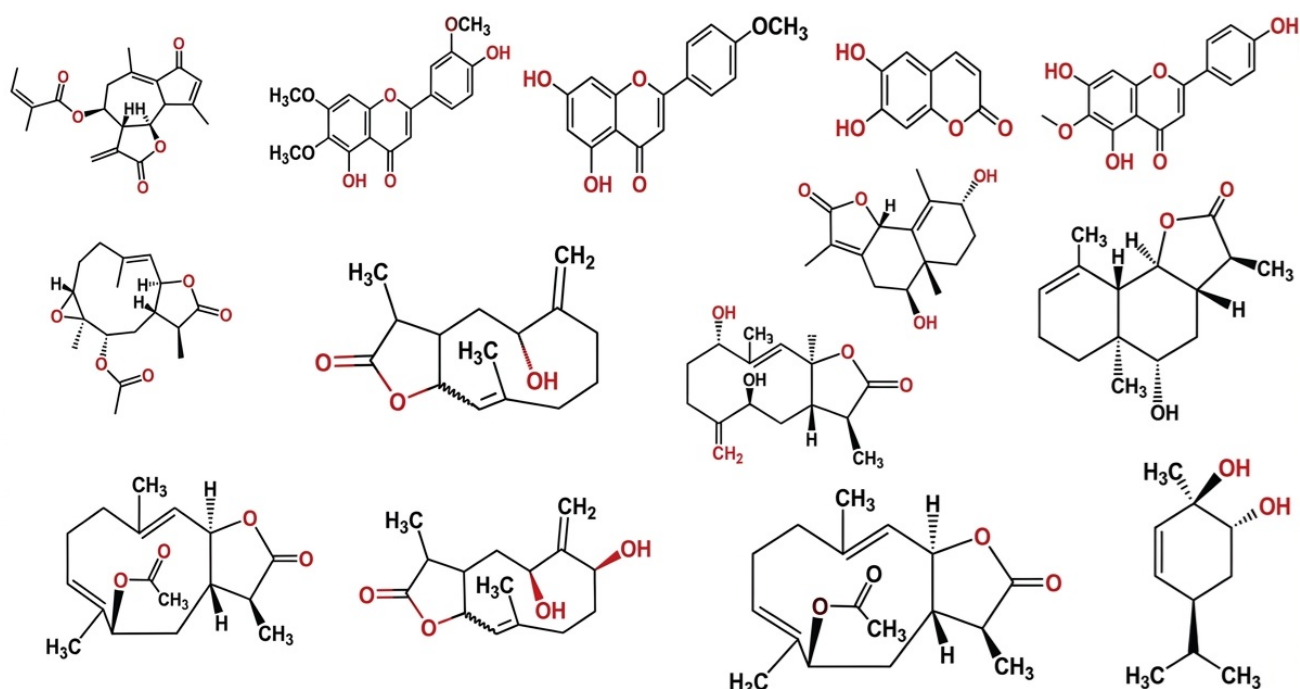


Fig. 2. Chemical structures of the identified bioactive compounds. Moxartenolide, Eupatrin, Acacetin, Esculetin, Hispidulin, Herbolide B, Herbolide H, Herbolide F, Herbolide E, Herbolide G, Herbolide C, Herbolide D, Herbolide A and 5-Methyl-2-methylene-4-vinyl-5-hexene-1,3-diol, respectively (from left to right and from top to bottom).

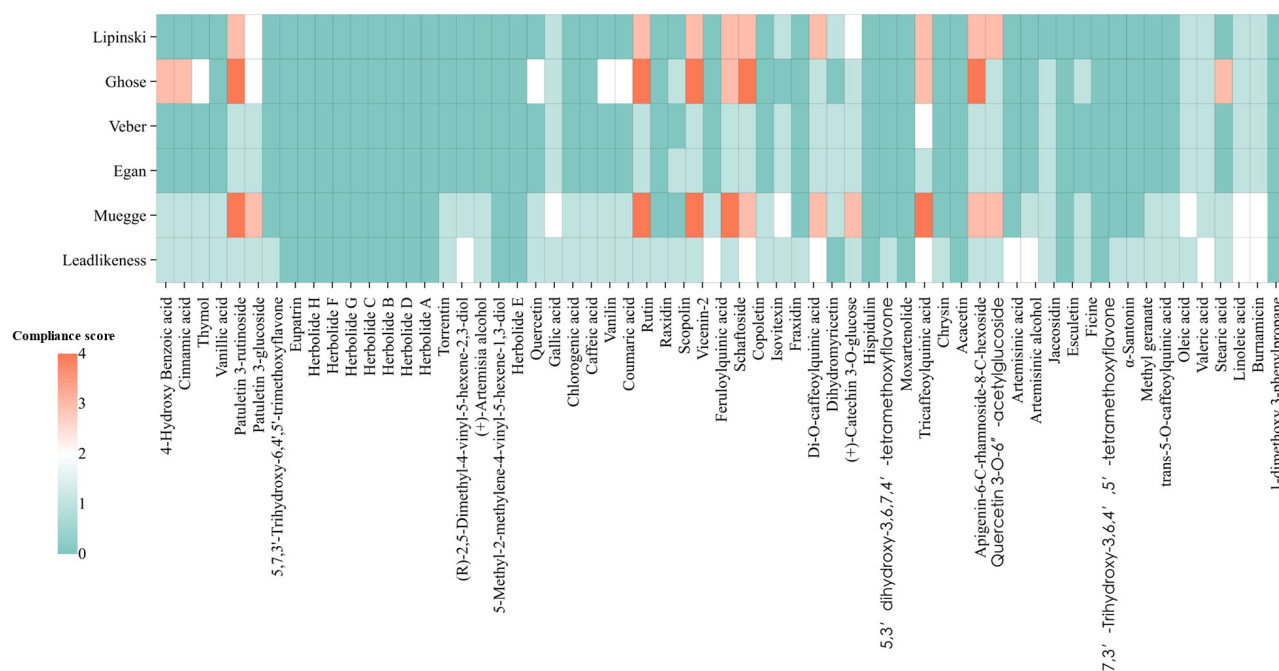


Fig. 3. Heatmap representing the drug-likeness and lead-likeness potential of *Artemisia* bioactive compounds based on established pharmacokinetic filters. The heatmap displays the degree of compliance with six commonly used medicinal chemistry filter rules (Lipinski, Ghose, Veber, Egan, Muegge, and Lead-likeness). Colors represent the number of rule violations per compound on a scale from 0 to 4: dark teal indicates 0 violations (full compliance), light teal indicates 1 violation, white indicates 2 violations, and light to deep coral red indicate 3 to 4 violations (increasing deviations). These violations indicate deviations from specified thresholds for molecular weight, hydrogen-bond donors and acceptors, lipophilicity (logP), topological polar surface area (tPSA), and rotatable bond count.

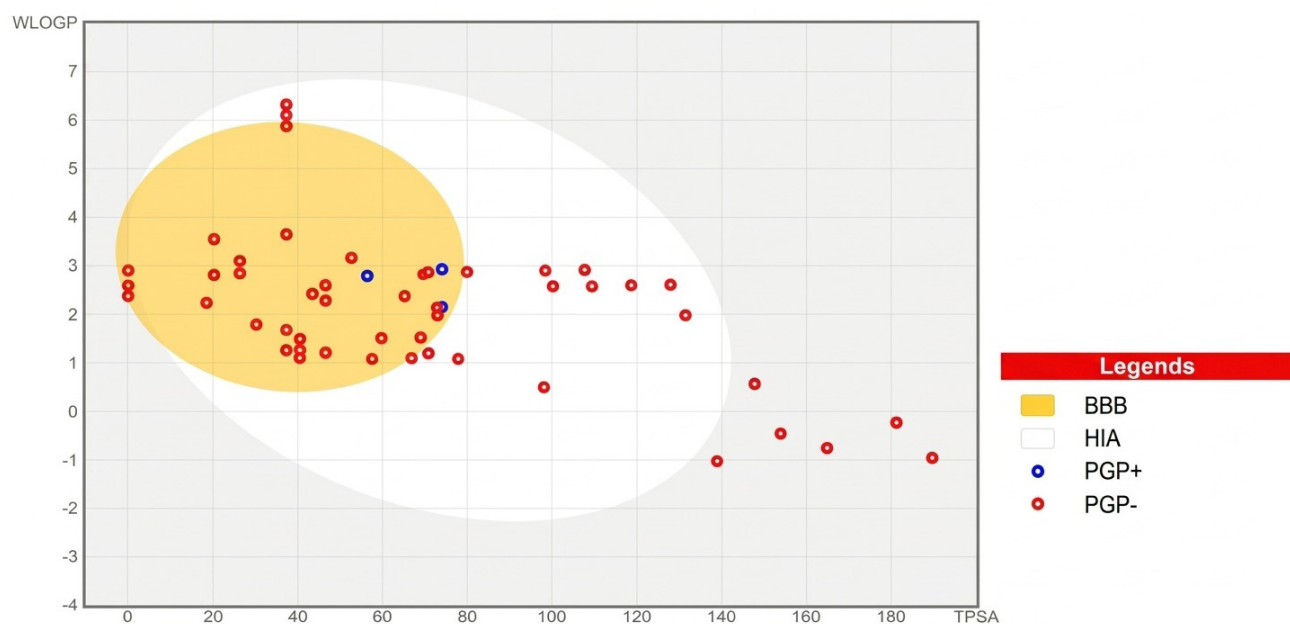


Fig. 4. Predicted absorption profiles of *Artemisia* bioactive compounds based on human intestinal absorption (HIA) and BBB permeability. The compounds located within the yellow region are predicted to exhibit high BBB permeation, whereas those within the white region have a high probability of passive gastrointestinal absorption. Compounds located in the grey/outer region are predicted to exhibit low gastrointestinal absorption and low BBB permeation. The y-axis represents WLOGP (lipophilicity), where positive values denote lipophilic character and negative values denote hydrophilic (or lipophobic) properties. BBB, blood-brain barrier; WLOGP, Wildman-Crippen lipophilicity; TPSA, Topological Polar Surface Area; PGP, P-glycoprotein.

three-dimensional (3D) atomic coordinates of the target proteins were retrieved from the RCSB Protein Data Bank (PDB; <https://www.rcsb.org/>); unresolved tertiary protein structures were predicted using AlphaFold. The 3D structures of the bioactive compounds were obtained from PubChem. The resulting protein-ligand complexes were analyzed for binding modes and intermolecular interactions using Discovery Studio 2017 R2 Client (v17.2.0.16349; <https://discover.3ds.com/discovery-studio-visualizer-download>) and UCSF Chimera v1.17.3 (<https://www.cgl.ucsf.edu/chimera/>).

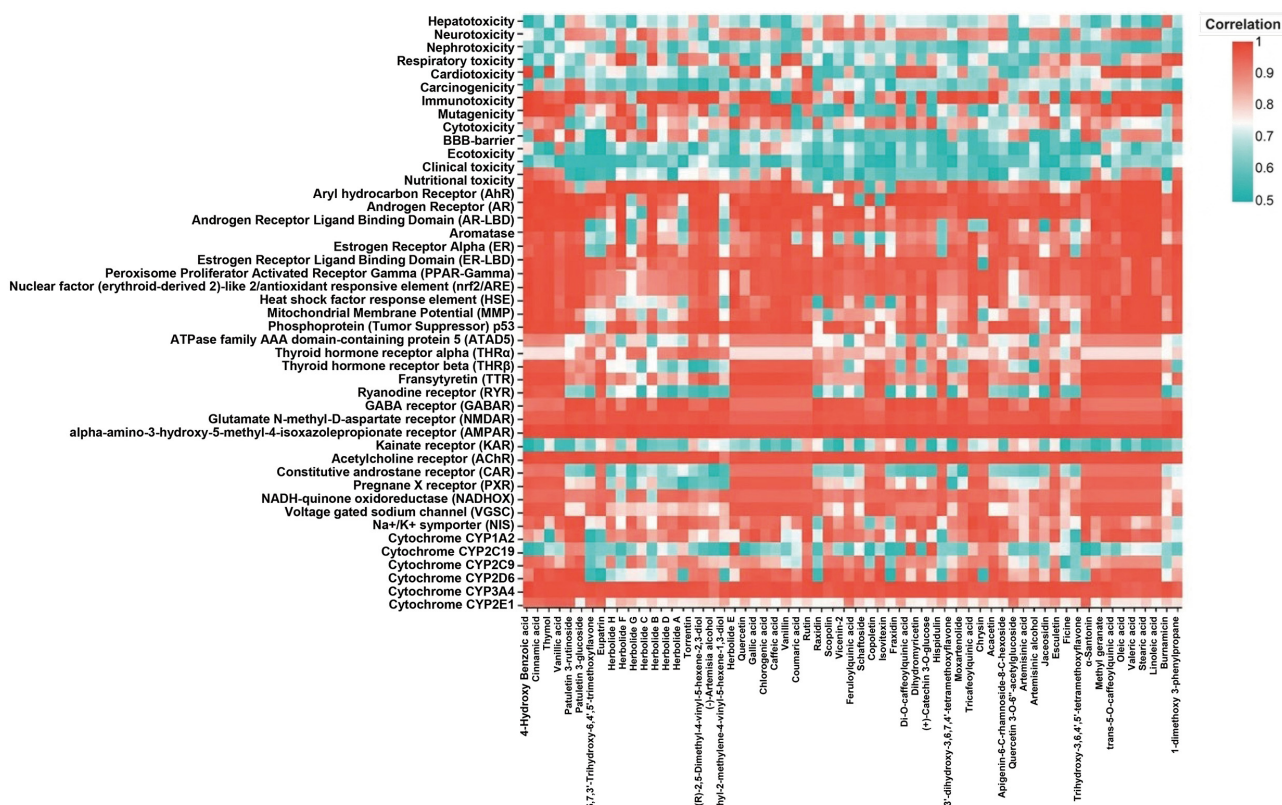
3. Results

A total of 108 compounds were initially identified, of which 62 had available structural data, 14 passed ADMET filtering, and 34 overlapping targets were retained. The multi-criteria prioritization of the leading phytochemicals identified through the integrated computational workflow is summarized in **Supplementary Table 2**.

3.1 Drug-likeness and Toxicity Profile of the Bioactive Compounds

Through extensive database searches and bibliographic mining, 108 compounds were identified in *Artemisia herba-alba*. Of these, only 62 canonical SMILES strings were successfully retrieved from PubChem. As shown in Fig. 2, 14 white wormwood compounds satis-

fied the predefined drug-likeness criteria and complied with Lipinski's Rule of Five (i.e., number of hydrogen bond donors (HBD) ≤ 5 , number of hydrogen bond acceptors (HBA) ≤ 10 , molecular weight (MW) < 500 Da, and $\log P \leq 5$) [22]. These 14 compounds also satisfied the criteria of the Ghose filter, which evaluates key physicochemical properties; Veber's rule, which considers molecular flexibility and topological polar surface area (TPSA); Egan's rule, which assesses absorption-related lipophilicity and TPSA; and Muegge's rule, which evaluates physicochemical and structural features relevant to drug-likeness. In addition, these compounds met the established lead-likeness criteria or optimized lead molecule selection (Fig. 3). Pharmacokinetic simulations of human intestinal absorption and blood-brain barrier (BBB) permeability (Fig. 4) were performed. Although structural information was available for 62 compounds, only 58 were successfully analyzed using the BOILED-Egg model because of SMILES input compatibility issues. The four compounds excluded from the analysis were benzoic acid, p-(β -D-glucopyranosyloxy)-methyl ester; di-O-caffeoylquinic acid; rosmarinic acid; and tricaffeoylquinic acid. The analysis revealed that: (i) 32 compounds were predicted to cross both the human intestinal and BBB, (ii) 18 compounds were predicted to be absorbed by intestinal cells without crossing the BBB, (iii) 8 compounds failed to penetrate either the intestine or the BBB. Toxicity assessments indicated that while some com-



pounds may interact with cell receptors, cytochrome P450 monooxygenases, ion channels and antioxidant response elements, none were predicted to have clinical toxicity effects, despite isolated predictions of organ-specific cytotoxicity or mutagenicity (Fig. 5).

Data mining identified 3414 AML-related targets, which were narrowed down to 524 unique gene identifiers after duplicate removal. Similarly, 755 bioactive targets for *Artemisia* were retrieved, resulting in 690 unique identifiers. A comparative analysis (Fig. 6) identified 34 overlapping genes that serve as common targets for both AML and the bioactive compounds present in *A. herba-alba*.

The protein-protein interaction (PPI) network of the 34 identified genes illustrates complex physical and functional interactions between their encoded proteins. This highlights the coordinated molecular mechanisms through which *A. herba-alba* bioactive compounds may modulate AML (Fig. 7). To identify the most influential compo-

3.4 Molecular Docking

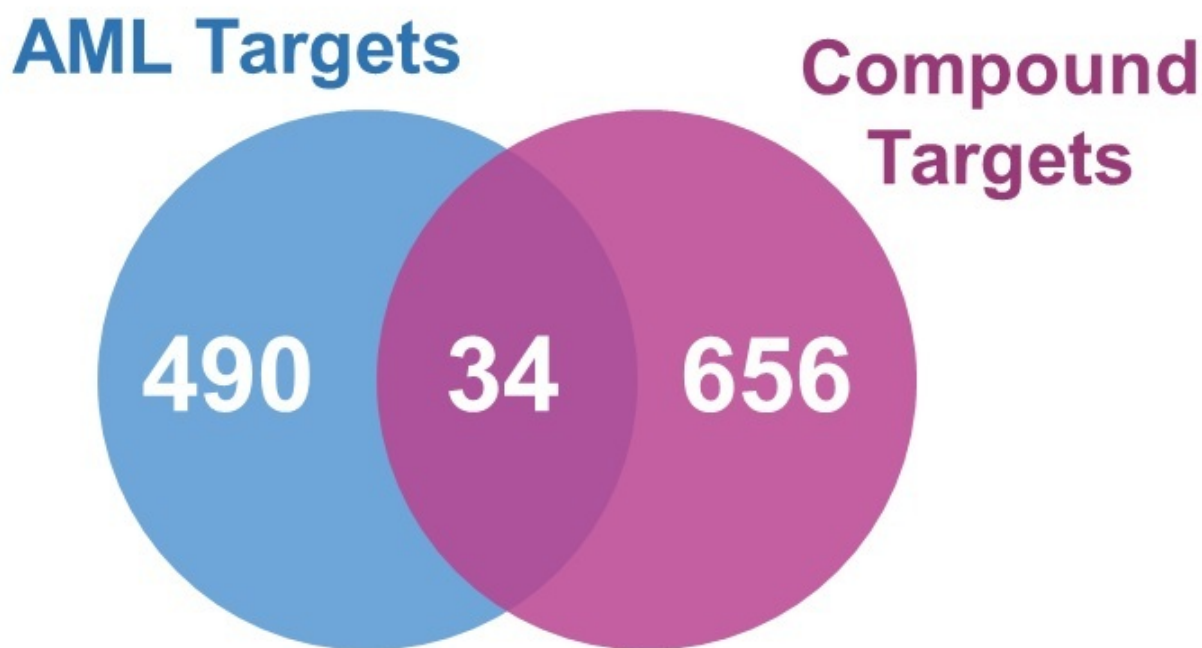


Fig. 6. Venn diagram illustrating overlapping target genes between AML and *Artemisia* bioactive compounds.

selected white wormwood bioactive compounds that satisfied drug-likeness, pharmacokinetic, and toxicity criteria. Potential ligand-binding pockets were identified and characterized using Discovery Studio Visualizer (<https://discover.3ds.com/tr/biovia-discovery-studio-simulation>) prior to docking. The predicted binding affinities for all protein-ligand complexes are summarized in Table 1. Representative top-ranked complexes are shown in 3D and 2D in Figs. 10,11, respectively.

Herbolide B consistently exhibited the strongest binding affinities across several independent hub proteins, suggesting promiscuous but biologically coherent polypharmacology. Docking alone does not demonstrate biological activity.

4. Discussion

4.1 Previous Studies on the Therapeutic Potential of *Artemisia*

A previous study by Ticolea et al. [23] highlighted the therapeutic potential of the *Artemisia* genus, attributing its broad pharmacological activity to a diverse phytochemical profile rich in flavonoids, alkaloids, phenolic compounds, and essential fatty acids. Extracts and isolated constituents from *Artemisia* species have been reported to exert antiproliferative, pro-apoptotic, anti-inflammatory, immunomodulatory, and antioxidant effects in both solid and hematological malignancies [24,25]. These activities are mediated through modulation of key signaling pathways, including PI3K/AKT/mTOR, cell-cycle regulatory networks, cytokine signaling, and oxidative stress responses.

Our findings are consistent with these observations and expand current knowledge by focusing specifically on AML, a disease for which *A. herba-alba* remains relatively underexplored. While earlier studies primarily assessed cytotoxicity and pathway-specific responses in general cancer cell lines, the present work adopts a systems pharmacology approach to link *A. herba-alba* phytochemicals directly with AML-associated molecular targets. By integrating physicochemical profiling, drug-likeness evaluation, and network-based target identification, this study provides mechanistic insight into how *Artemisia* compounds may exert anticancer effects beyond single-pathway modulation, supporting their therapeutic potential in complex, heterogeneous malignancies such as AML.

4.2 Validation of Identified Hub Targets

Network analysis identified potassium channels, phospholipase A2 (PLA2), cytochrome P450 monooxygenases (CYPs) involved in xenobiotic biotransformation, and arachidonate-5-lipoxygenase (ALOX5) as central hub targets linking *A. herba-alba* phytochemicals to AML-related pathways. These targets are well-supported by existing literature as essential regulators of cell proliferation, survival, metabolism, inflammation, and treatment resistance.

Potassium channels are critical regulators of membrane excitability and intracellular signaling; their dysregulation is increasingly associated with oncogenesis. In leukemia and various solid tumors, aberrant potassium channel activity has been associated with altered

Table 1. Predicted binding affinities (in kcal/mol) of candidate *Artemisia* bioactives against the predicted hub proteins.

	PLA2G1B (PDB:6Q42)	KCNQ1 (PDB:9U7F)	ALOX5 (PDB:3V99)	KCNH2 (PDB: 6SYG)	PLA2G4A (AF-P47712-F1)	PLA2G2A (PDB:3U8I)	KCNK2 (4TWK)	PLA2G6 (AF-O60733-F1)	KCNJ5 (AF-P48544-F1)	CYP11B1 (PDB:6M7X)
Moxartenolide	-8.3	-7.3	-8	-5.8	-6.3	-8.4	-8.9	-5.5	-6.2	-8.6
Eupatrin	-6.5	-7.3	-7.1	-5.6	-6.2	-7.7	-7.7	-6.6	-7.4	-8.1
Acacetin	-7.3	-7.5	-7.4	-5.8	-6.1	-7.9	-8.1	-8.1	-6.3	-8.7
Esculetin	-7.1	-5.9	-7.3	-4.8	-5.1	-6.7	-6.6	-5.6	-4.8	-7
Hispidulin	-7.3	-7.4	-7.5	-5.5	-6.2	-7.9	-7.7	-5.8	-6.8	-8.5
Herbolide B	-7.4	-9	-9.1	-6.7	-7	-9.3	-10.5	-6.6	-8.1	-9.3
Herbolide H	-6.1	-5.8	-4.4	-4.2	-3.8	-5.9	-7.7	-4.1	-5.1	-6
Herbolide F	-6.2	-5.7	-6.5	-4.3	-4.7	-6.4	-6.1	-4.5	-5.6	-6.5
Herbolide E	-5.2	-5.1	-5.4	-3.9	-4.7	-5.3	-5.6	-4.5	-4.3	-5.3
Herbolide G	-7.9	-6.5	-6.6	-5.1	-5.7	-7.1	-7.7	-6.4	-5.4	-7.5
Herbolide C	-7.5	-6.5	-5.8	-5.5	-5.4	-7.6	-7.2	-5.6	-5.5	-7.9
Herbolide D	-6.1	-6.8	-6.3	-5.2	-6	-7.6	-7.9	-5.9	-5.6	-7.8
Herbolide A	-7.5	-6.7	-6.7	-5.5	-5.7	-8.3	-7.9	-6.1	-6	-8
MMVHD	-5.4	-4.5	-5	-3.6	-4.5	-5.3	-5.6	-2.6	-4.7	-5.4

MMVHD, 5-Methyl-2-methylene-4-vinyl-5-hexene-1,3-diol; KCNH2, Potassium voltage-gated channel subfamily H member 2; KCNJ5, Potassium inwardly rectifying channel subfamily J member 5; PLA2G1B, Phospholipase A2 group IB; CYP11B1, Cytochrome P450 family 11 subfamily B member 1; KCNQ1, Potassium voltage-gated channel subfamily Q member 1; ALOX5, Arachidonate 5-lipoxygenase; PLA2G2A, Phospholipase A2 group IIA; PLA2G4A, Phospholipase A2 group IVA; PLA2G6, Phospholipase A2 group VI; KCNK2, Potassium two pore domain channel subfamily K member 2.

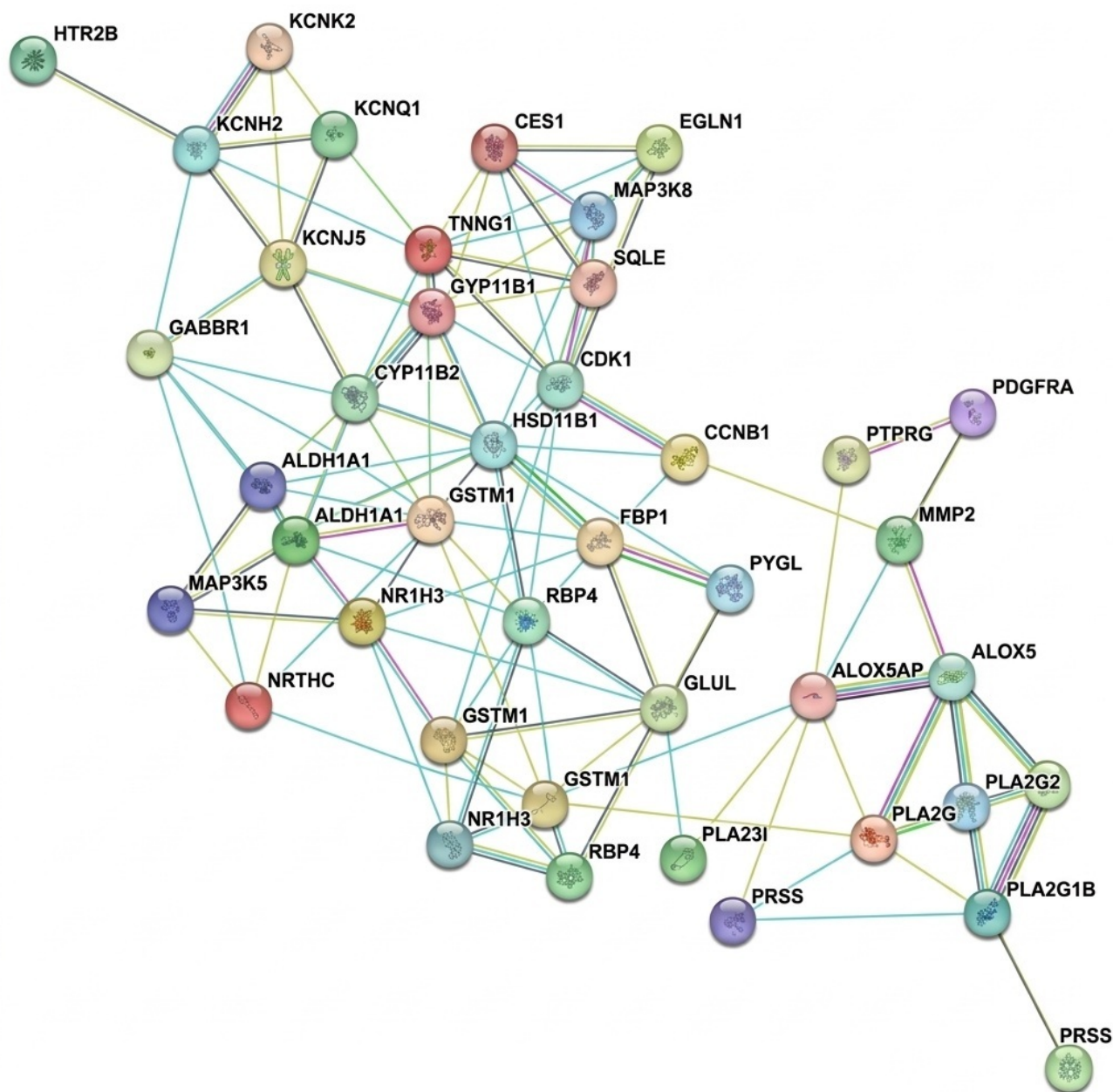


Fig. 7. Protein-protein interaction (PPI) network of the shared target gene products. The connecting lines (edges) are color-coded according to the type of evidence supporting the interactions: Purple, experimental evidence; Light blue, database evidence; Yellow, text-mining evidence; Dark grey, co-expression evidence; Green, gene neighborhood evidence; and Dark blue, gene co-occurrence evidence.

cell-cycle progression, resistance to apoptosis, migration and invasion, metabolic reprogramming, and angiogenesis [24,25,26]. Specific subtypes, including the KCNQ, KCNJ, KCNH, and KCNK families, have been implicated in tumor growth and poor prognosis, highlighting their value as both biomarkers and therapeutic targets.

PLA2 enzymes regulate lipid signaling by generating bioactive fatty acids and lysophospholipids that feed into oncogenic pathways. Altered lipid metabolism is a recognized hallmark of AML, particularly within leukemia stem cells. Of note, PLA2G4A has been linked to *FLT3-ITD*-

driven leukemogenesis; its inhibition suppresses leukemic cell growth and modulates the immunosuppressive tumor microenvironment [27,28,29,30]. The identification of PLA2 isoforms as hub targets underscores their emerging role as viable therapeutic nodes in AML.

ALOX5, a key enzyme in arachidonic acid metabolism, contributes to the production of leukotrienes and other lipid mediators involved in inflammation and tumor progression [31,32]. Both genetic and pharmacological inhibition of ALOX5 has been shown to induce cell-cycle arrest, promote apoptosis and disrupt tumor-

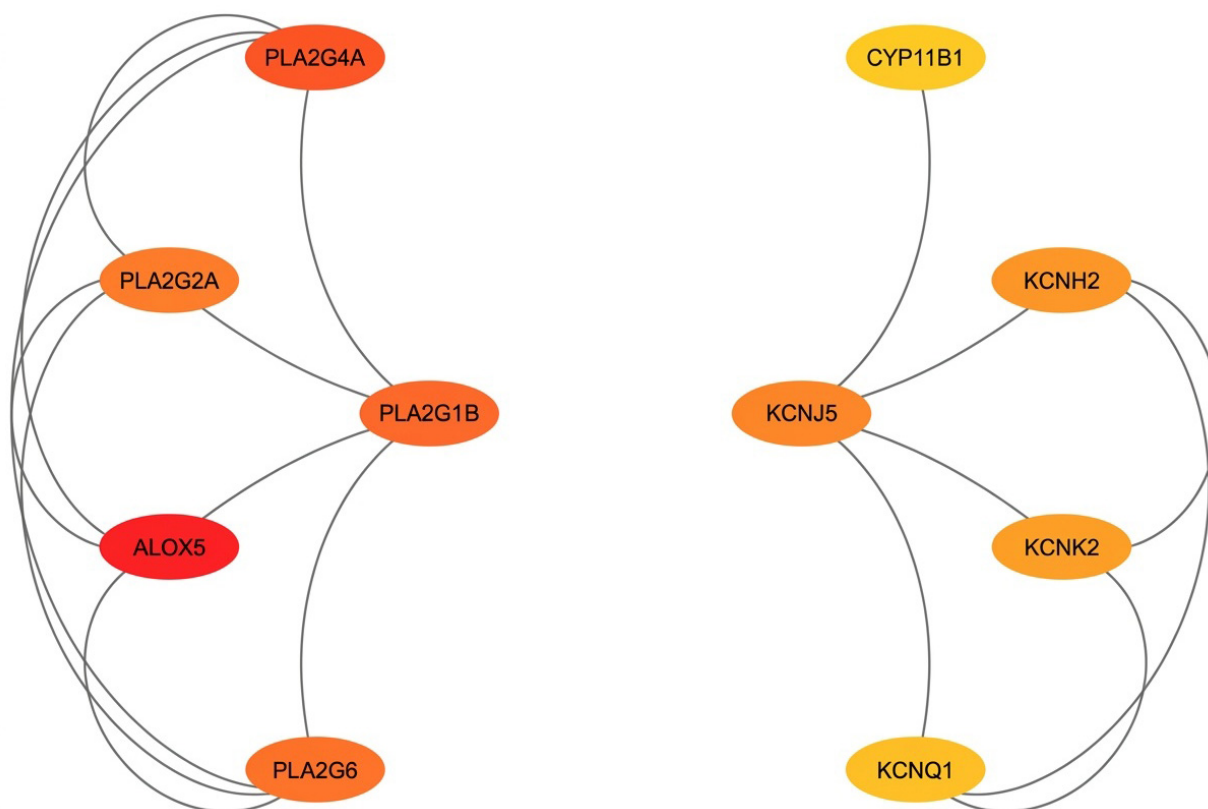


Fig. 8. The top ten hub proteins within the PPI network.

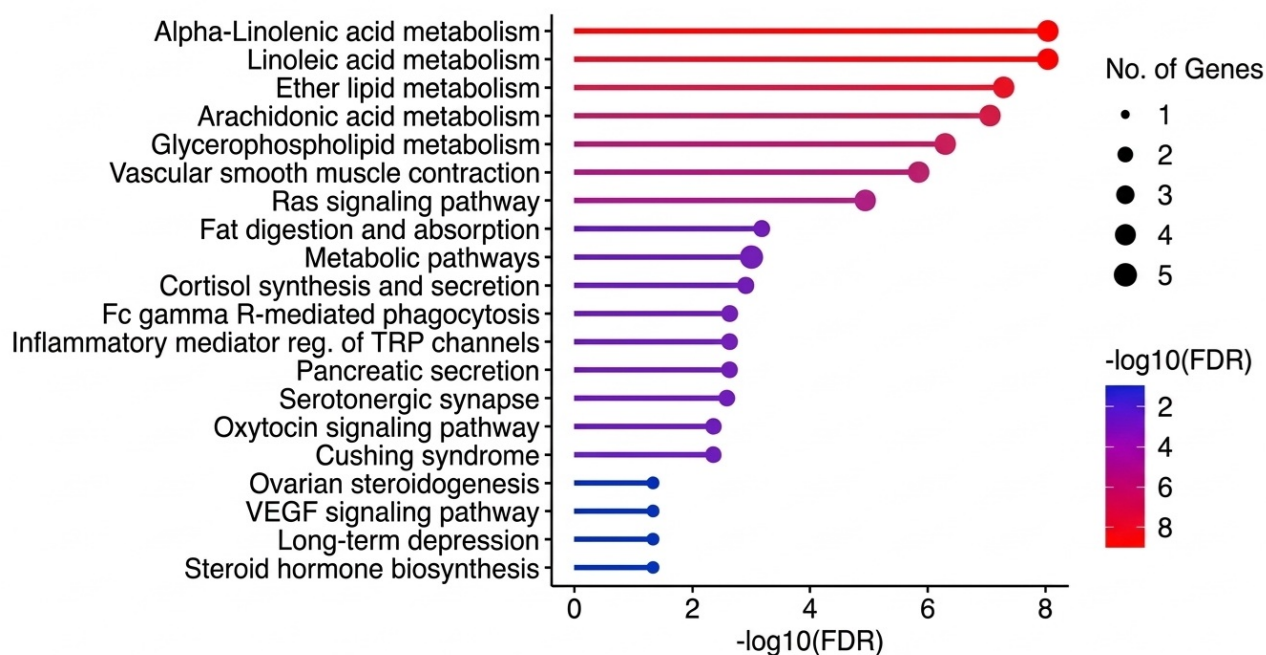


Fig. 9. Over-represented KEGG biological pathways associated with the identified hub genes. FDR, false discovery rate, calculated using the Benjamini–Hochberg correction.

microenvironment interactions in several cancer models, including hematological malignancies [33,34,35]. The identification of ALOX5 as a network hub suggests that *A.*

herba-alba phytochemicals may exert anticancer effects by modulating inflammatory and lipid-mediated signaling relevant to AML.

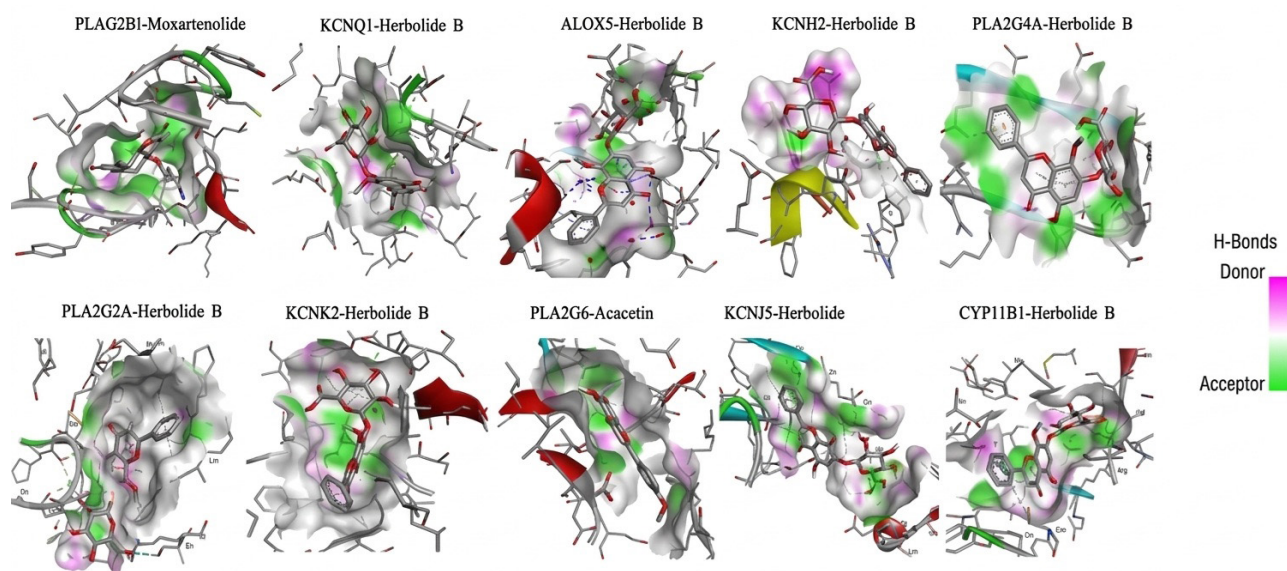


Fig. 10. Molecular docking visualizations showing binding-site interactions between selected *Artemisia* compounds and their respective target proteins.

CYP monooxygenases play a dual role in cancer biology by regulating hormone metabolism, lipid mediator synthesis, and xenobiotic biotransformation. Alterations in CYP activity contribute to carcinogenesis, variability in drug response, and resistance to chemotherapy [36,37,38,39]. Since many anticancer agents are CYP substrates, the modulation of these isoforms can significantly influence therapeutic efficacy and toxicity. The predicted interactions between *A. herba-alba* compounds and multiple CYP isoforms highlight their potential to influence both endogenous oncogenic processes and drug metabolism.

4.3 Therapeutic Implications for AML

Despite advances in targeted and combination therapies, AML remains a clinically challenging disease characterized by pronounced genetic heterogeneity, treatment-related toxicity, frequent relapse, and the persistence of quiescent leukemia stem cells. Most current therapeutic strategies rely on highly selective targets; however, these often fail to eradicate stem cell populations and can inadvertently facilitate the emergence of resistance. Consequently, there is growing interest in polypharmacological approaches capable of simultaneously modulating multiple oncogenic pathways.

The present study identifies *Artemisia herba-alba* as a promising source of polypharmacological agents capable of modulating interconnected AML-relevant pathways. The identified phytochemicals demonstrate the potential to modulate interconnected biological processes, including ion transport, lipid metabolism, inflammatory signaling, and xenobiotic processing, that collectively contribute to AML initiation, progression, and therapy resistance.

Targeting potassium channels, PLA2, ALOX5, and CYPs may complement existing AML therapies by enhancing drug sensitivity, disrupting leukemia stem cell maintenance, and mitigating the development of resistance. This multi-target approach aligns with emerging evidence that synergistic strategies improve treatment durability, similar to combination approaches currently used to overcome venetoclax resistance [40]. Collectively, these findings provide a strong rationale for further experimental validation of *A. herba-alba*-derived compounds as both standalone lead candidates and adjuvants to conventional AML treatments, aiming to achieve more durable remissions and improved patient outcomes.

Importantly, unlike many network pharmacology studies that rely exclusively on target prediction or docking, the present work integrates phytochemical curation from multiple experimental reports, ADMET screening, transcriptomic AML datasets, disease-associated databases, protein interaction analysis, pathway enrichment and molecular docking into a unified prioritization pipeline. The convergence of these independent computational evidence layers and the resulting prioritization of lead compounds are summarized in **Supplementary Table 2**. Rather than identifying isolated compound-target interactions, this framework converges independent computational evidence to nominate biologically plausible therapeutic hypotheses. Such prioritization is increasingly recognized as an essential step in modern drug discovery, where experimental screening of hundreds of natural compounds is financially and technically impractical. Consequently, this study provides a rational roadmap for directing future experimental resources toward the most promising *Artemisia*-derived candidates.

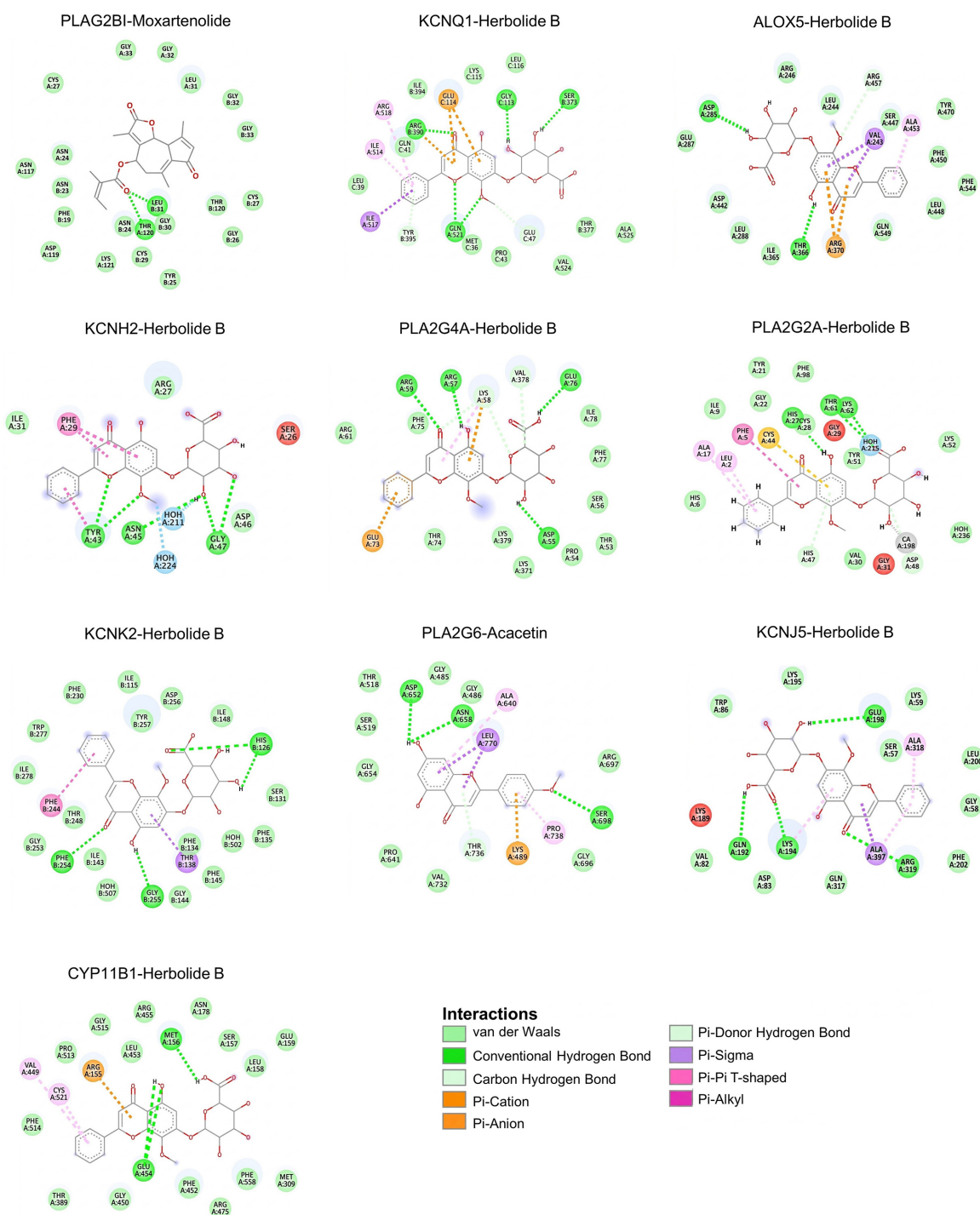


Fig. 11. Detailed 2D representations of key interacting amino acid residues within the target protein binding pockets for the top-ranked *Artemisia* compounds.

4.4 Study Limitations

The primary limitation of this study is its entirely computational nature. The findings rely on *in silico* predictions without *in vitro* or *in vivo* experimental validation to confirm the proposed anti-AML activities of the identified phytochemicals.

AML is a highly heterogeneous malignancy characterized by diverse molecular and cytogenetic subtypes. Consequently, the generalized set of 34 overlapping genes identified in this study may not be equally relevant across all AML subtypes or patient populations.

In addition, AML-associated genes were derived from multiple transcriptomic datasets that vary in sequencing platforms, sample sizes, patient heterogeneity, and pre-processing pipelines. Such variability may introduce biases and affect the overall robustness of the identified gene set. Moreover, the application of stringent thresholds ($\log_2\text{FoldChange} \geq 2$) may have excluded genes with moderate yet biologically meaningful expression changes. Nevertheless, these strict criteria were deliberately employed to reduce false positives and prioritize the most significantly dysregulated genes, thereby enhancing the reliability of the selected targets.

Furthermore, for target proteins lacking experimentally resolved tertiary structures, AlphaFold-predicted models were utilized. Although these models are highly accurate, they may not fully capture native conformational dynamics, binding pocket architecture, or protein flexibility. This limitation introduces a degree of uncertainty in the interpretation of ligand-target interactions.

5. Conclusions

Artemisia herba-alba represents a rich source of phytochemicals with promising yet largely unexplored therapeutic potential against acute myeloid leukemia (AML). Integrated pharmacokinetic analyses identified several bioactive constituents with favorable drug-like properties, including predicted oral bioavailability, appropriate systemic disposition, CYP-mediated metabolism, and low toxicity. Network pharmacology further implicated these compounds in biological processes central to AML pathogenesis, particularly lipid metabolism, hormonal signaling, immune regulation, and inflammatory pathways. Molecular docking prioritized herbolide B, acacetin, and moxartenoide as high-affinity binders of key AML-associated proteins, highlighting their potential as multi-target therapeutic candidates. More broadly, this study establishes a reproducible computational framework that integrates pharmacokinetic profiling, network pharmacology, transcriptomic evidence, and structure-based modeling to efficiently prioritize natural products for anticancer drug discovery. By substantially reducing the experimental search space, this strategy is readily applicable to other medicinal plants and hematological malignancies. Collectively, these findings support the further investigation of *A. herba-alba*-derived phytochemicals as promising multi-target agents for the treatment of AML.

Abbreviations

AML, Acute myeloid leukemia; CYPs, Cytochrome P450 monooxygenases; PLA2, Phospholipase A2; KCNH2, Potassium voltage-gated channel subfamily H member 2; KCNJ5, Potassium inwardly rectifying channel subfamily J member 5; PLA2G1B, Phospholipase A2 group IB; CYP11B1, Cytochrome P450 family 11 subfamily B member 1; KCNQ1, Potassium voltage-gated

channel subfamily Q member 1; ALOX5, Arachidonate 5-lipoxygenase; PLA2G2A, Phospholipase A2 group IIA; PLA2G4A, Phospholipase A2 group IVA; PLA2G6, Phospholipase A2 group VI; KCNK2, Potassium two pore domain channel subfamily K member 2.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request. Publicly available datasets used in this study can be accessed through GEO and other public databases as described in the Methods section.

Author Contributions

Conceptualization, BS and AP; methodology, BS and AP; software, BS; validation, BS and AP; formal analysis, BS, AGG and AP; data curation, BS; writing—original draft preparation, BS, AGG and AP; writing—review and editing, BS, AGG and AP; supervision, AP; project administration, AP. All authors have read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to express our sincere gratitude to all peer reviewers for their constructive comments and valuable suggestions, which helped improve the quality of this work.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest. Given his role as the Guest Editor and Editorial Board member, Alexandros G Georgakilas had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/FBL56143>.

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