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Research on the Mechanism of Si Xian Decoction in Treating Acute Leukemia Based on Network Pharmacology and Molecular Docking Technology

Zihan Jiang[1] Man Zhang[1] Jiayuan Guo[1] Mingxin Liu[1] Wenqing Liu[1] Jue Guo[1] Qiuling Ma[1,2]

[1] The Second Clinical Medical School, Henan University of Chinese Medicine, Zhengzhou, Henan, China
[2] Institute of Hematology, Henan Province Hospital of TCM (The Second Affiliated Hospital of Henan University of Chinese Medicine), Zhengzhou, Henan, China

Address for correspondence Qiuling Ma, PhD, The Second Clinical Medical School, Henan University of Chinese Medicine, 156 Jinshui East Road, Zhengzhou, Henan 450046 China (e-mail: ling93317@163.com).

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Abstract

Objective Our objective was to investigate the mechanism of action of the Si Xian Decoction (SXD) in treating acute leukemia (AL) using network pharmacology and molecular docking techniques.

Methods The chemical components of the four medicinal herbs of Shengdi (Rehmanniae Radix), Baimaogen (Imperatae Rhizoma), Xiaoji (Cirsii Herba), and Pugongying (Taraxaci Herba) in the SXD were obtained from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine (BATMAN-TCM), and Encyclopedia of Traditional Chinese Medicine (ETCM). A natural active chemical component dataset for the SXD was established. Human Gene Database (Gencards), Database of Gene-Disease Associations (DisGeNET), Database for Drug and Drug Target Information (DrugBank), and Human Disease Database (MalaCards) were searched to obtain AL-related targets and to establish a disease target database. After obtaining the intersection targets of drugs and diseases, a Venn diagram of the common targets was drawn online. A drug-disease protein interaction network was constructed using the String 11.5 platform, and a "drug-disease-target-signal pathway" network was built using Cytoscape 3.8.2 software to obtain relevant target network topology parameters.

Results By searching the TCMSP, BATMAN-TCM, and ETCM databases, 30 active components of the SXD and 677 related targets were obtained. From Gencards, DrugBank, MalaCards, and DisGeNET databases, 12,110 potential AL disease targets were obtained. Using the ClusterProfiler package of the R4.2.2 platform, 1,011 entries of gene ontology information were enriched, including 467 biological process entries, 236 molecular function entries, and 308 cellular component entries. Additionally, 220 enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways were

Keywords
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- Si Xian decoction
- fresh herbs
- network pharmacology
- action mechanism

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obtained, mainly involving chemical carcinogen receptor activation, lipid and atherosclerosis, fluid shear stress and atherosclerosis, prostate cancer, and the role of the advanced glycation end products-receptor for advanced glycation end products (AGE-RAGE) signaling pathway in diabetic complications. Network topology analysis revealed that the main active components of SXD treating AL include γ-aminobutyric acid, adenosine, quercetin, scopolamine, and taraxasterol.

Conclusion The treatment of AL with the SXD is a process of multicomponent, multitarget, and multisignal pathway coordination. Network pharmacology provides a solid research basis for elucidating the mechanism of action of SXD in the treatment of AL.

Introduction

The characteristic of acute leukemia (AL) is the abnormal proliferation and differentiation inhibition of leukemia progenitor cells and immature cells in the bone marrow,[1] which is a common malignant tumor related to hematopoietic stem cells. In 2021, there were 25,930 diagnosed cases of AL patients in the United States, with 12,980 deaths among AL patients.[2] In traditional Chinese medicine (TCM), it is believed that the pathogenesis of AL is similar to the development pattern of warm diseases in Chinese medicine. In the early stage of the disease, there is excessive toxic heat, with symptoms such as sudden high fever and even severe bleeding, mainly characterized by heat accumulation, falling under the categories of "acute exertion" and "heat exertion" in terms of disease patterns. TCM has advantages in the treatment for AL with the methods of clearing heat and detoxifying, nourishing yin, and cooling blood.[3] For instance, Academician Chen discovered the effective component for treating acute promyelocytic leukemia—arsenic trioxide in the Chinese medicine arsenic and conducted detailed research on the molecular mechanisms of this effective active ingredient.[4]

Si Xian Decoction (SXD) is a good prescription for treating AL, as described in Yimin Sun's *Clinical Medical Cases and Prescriptions (Lin Zheng Yi An Yi Fang)*. Professor Sun used high doses of fresh herbs to treat warm and heat diseases, showing significant efficacy without adverse reactions.[5] Based on the characteristics of warm diseases such as heat, dampness, and yin damage, fresh herbs are mostly sweet and cold in nature, making them particularly suitable for treating warm diseases and can be used from the early stages to the later stages of the disease.[6] SXD is composed of four fresh Chinese herbs: Shengdi (Rehmanniae Radix), Baimaogen (Imperatae Rhizoma), Xiaoji (Cirsii Herba), and Pugongying (Taraxaci Herba). While expelling pathogenic factors, it also supports healthy qi of the body. It possesses functions such as clearing heat and removing toxin, nourishing yin and cooling blood, calming collaterals, and stopping bleeding. Professor Yimin Sun treated 76 patients with AL using SXD, achieving a complete remission rate of 48.7%, a partial remission rate of 18.4%, and an overall remission rate of 67.1%.[7] Related studies have shown that in a mice model of acute myeloid leukemia (AML; WEHI-3), after administering different doses of the SXD for 14 consecutive days, the results indicated that the fresh herb juice of SXD significantly increased the levels of CD3 and CD19 in mice, showing a good therapeutic and improvement effect on the model of AML cells in mice.[8]

Currently, there are limited basic research and clinical studies on the SXD, and its action mechanism in treating AL has not been fully elucidated. This study uses network pharmacology and molecular docking techniques to investigate the action mechanism of SXD in the treatment of AL.

Materials and Methods

Chemical Composition of the Si Xian Decoction and Screening of Relevant Targets

The Bioinformatics Analysis Tool Platform for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM, http://bionet.ncpsb.org/batman-tcm/), the Encyclopedia of Traditional Chinese Medicine (ETCM, http://www.tcmip.cn/ETCM/index.php/Home/Index/) database, and the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php) were used to retrieve and obtain the chemical composition of the four herbs (Shengdi [Rehmanniae Radix], Baimaogen [Imperatae Rhizoma], Xiaoji [Cirsii Herba], and Pugongying [Taraxaci Herba]) in the SXD and establish a dataset of active chemical components in the SXD. The names of important active components obtained from the above processing were imported into the protein interaction database String (https://cn.string-db.org/) for searching, and the chemical component names were replaced with target names. The chemical names that were not successfully identified were imported into the Universal Protein (Uniprot, http://www.uniprot.org) database to obtain all targets, and duplicate targets were removed to obtain the final SXD-related targets.

Screening of Target Genes for Acute Leukemia Diseases

The keyword "Acute leukemia" was used to search for relevant target genes in the Human Gene Database (GenCards, https://www.genecards.org), Database for Drug and Drug Target Info (DrugBank,https://www.drug-bank.ca), the Human Disease Database (MalaCards, https://www.malacards.org), and the Database of Gene-Disease Associations

(DisGeNET, https://www.disgenet.org). 9 Duplicate targets were removed to establish a database.

Intersection Screening of "Drug–Disease" Common Targets and Construction of Protein–Protein Interaction Network

The drug targets of the SXD and the AL disease targets were imported into the online Venn diagram maker (http://bioinformatics.psb.ugent.be/webtools/Venn/) to obtain the intersection targets of "drug–disease" common targets, which are key targets for the treatment of AL by active ingredients of the SXD, and a Venn diagram was drawn. The interaction relationship between the common intersection targets of "drug–disease" was analyzed using the String 11.5 database, and the data were imported into Cytoscape 3.8.2 software for topological analysis to obtain the protein-protein interaction (PPI) network.

Functional Analysis and Visualization of Key Targets

Gene ontology (GO) defines and describes gene product functions from three aspects: biological process (BP), cellular component (CC), and molecular function (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG) defines and describes gene product functions from the aspects of genome, chemistry, and system functionality. To obtain more accurate gene function enrichment information, this study used the ClusterProfiler package in the R4.2.2 platform to visualize the obtained data, obtaining GO and KEGG functional enrichment analysis results and adjusting the screening criteria to $p \leq 0.05$, $q \leq 0.01$. The top eight entries were plotted as a GO chord diagram (including three components: BP, CC, and MF) and KEGG signal pathway enrichment bubble diagram and KEGG signal pathway enrichment chord diagram.

Construction of "Drug–Disease–Target–Signal Pathway" Network

Cytoscape 3.8.2 software was used to construct the "Drug–Disease–Target" network to obtain a visual network.

Molecular Docking Verification

Using the Schrodinger software, the top 3 degree values (in the "disease-drug component-target" network) of the main active ingredients of the SXD and the top 3 ranked core proteins (in the PPI network) were subjected to molecular docking verification. The binding situation was analyzed, and the binding energy was calculated.

Results

Active Ingredients and Targets of the Si Xian Decoction

Through the built-in filters of the TCMSP, BATMAN, and ETCM databases restricting the values of oral bioavailability and drug likeness, a total of 31 chemical components were obtained, including 13 from Baimaogen (Imperatae Rhizoma), 3 from Shengdi (Rehmanniae Radix), 8 from Pugongying (Taraxaci Herba), and 7 from Xiaoji (Cirsii Herba), resulting in 30 active ingredients of the SXD after removing duplicate components among the four Chinese herbs. Using the Uniprot database, 677 target proteins related to the 30 effective active ingredients of the SXD were identified after replacing the targets of action and eliminating duplicates (►**Table 1**).

Table 1 Information on active ingredients of the SXD

Source	Marker	Chemical compound
Baimaogen (Imperatae Rhizoma)	HBMG1 HBMG2 HBMG3 HBMG4 HBMG5 HBMG6 HBMG7 HBMG8 HBMG9 HBMG10 HBMG11 HBMG12 A1(HBMG13)	6-Methoxyflavone anemonin donaxin β-sitosterol diphenyl ester colchicine imperatorin apocynin elisabetta ferrero luteolin colchicine demecolcine stigmasterol
Shengdi (Rehmanniae Radix)	HDH1 HDH2 HDH3	adenine nucleoside catalpol γ-aminobutyric acid
Pugongying (Taraxaci Herba)	HPGY1 HPGY2 HPGY3 HPGY4 HPGY5 HPGY6 HPGY7 HPGY8	taraxasterol chrysanthemaxanthin choline esculetin scopolamine caffeine taraxeryl flavoxanthin
Xiaoji (Cirsii Herba)	HXJ1 HXJ2 HXJ3 HXJ4 A2(HXJ5) HXJ6 HXJ7	robinin linarin quercetin sitosterol stigmasterol protocatechualdehyde 3, 4-dihydroxybenzoic acid

Note: β-sitosterol is a common active ingredient in Baimaogen (Imperatae Rhizoma) and Xiaoji (Cirsii Herba).

Acute Leukemia Disease Targets

Using "Acute leukemia" as a keyword, 12,039, 13, 465, and 639 potential targets for AL were, respectively, retrieved from the Gencards, DrugBank, MalaCards, and DisGeNET disease target databases. After removing duplicate targets, a total of 12,110 potential targets for AL disease were obtained.

Protein–Protein Interaction Network Among Common Drug–Disease Targets

An online Venn diagram platform was used to map the 677 active ingredient targets of the SXD with the 12,110 AL disease targets, resulting in a Venn diagram showing 517 common drug–disease intersection targets. These intersection targets were then imported into the Sting 11.5 database to construct a PPI network, which consisted of 516 nodes and 8,927 edges. The size of the nodes reflected the Degree value,

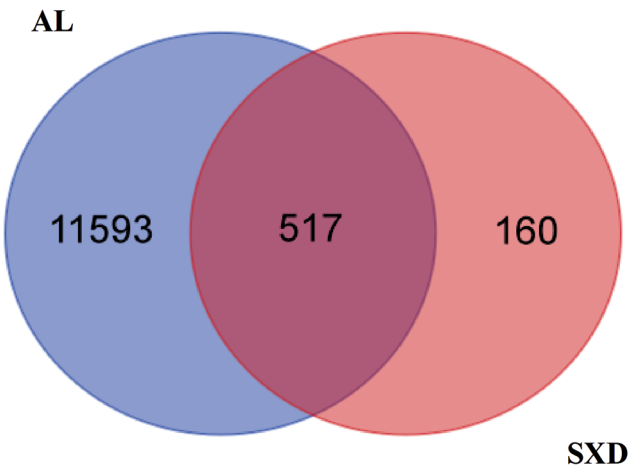


Fig. 1 Venn diagram of common drug–disease targets.

indicating their involvement in BPs. The larger the node, the darker the color, indicating a higher Degree value. This allowed for the identification of the active ingredients and core targets through which the SXD exerts its therapeutic effects on AL. Finally, Cytoscape 3.8.2 software was used for a more intuitive visualization adjustment (►**Figs. 1** and **2**). The protein interaction network between the SXD and AL showed that in the occurrence and development of AL, targets such as GAPDH, ACTB, and TP53 had the highest degree of freedom values and thus exerted significant effects.

Gene Ontology Biological Function and Kyoto Encyclopedia of Genes and Genomes Pathway Enrichment Analysis

In order to further elucidate the mechanism of the SXD in treating AL, the ClusterProfiler package of the R4.2.2 platform was used to perform GO biological function enrichment analysis and KEGG pathway enrichment analysis on 517 "drug–disease" intersection targets. The main screening criteria were set as $p \leq 0.05$ and $q \leq 0.01$. A total of 1,011 GO entries were obtained, including 467 BP entries, 236 MF entries, 308 CC entries, and 220 KEGG signal pathway entries. The top eight entries for BP, MF, CC, and KEGG signal pathways were plotted separately.

The BP category mainly involved cellular response to xenobiotic stimulus, gland development, response to metal ion, and response to nutrient and wound healing (►**Fig. 3**). There were 236 MF entries, mainly involving DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription factor binding, ubiquitin-like protein ligase binding, nuclear receptor activity, and amino acid binding (►**Fig. 4**). The CC category included 308 entries, primarily related to apical part of cell, integral component of postsynaptic membrane, membrane raft, neuronal cell body (►**Fig. 5**).

The KEGG analysis mainly involved chemical carcinogenesis receptor activation, lipid and atherosclerosis, fluid shear stress and atherosclerosis, prostate cancer, and the role of the advanced glycation end products-receptor for advanced glycation end products (AGE-RAGE) signal pathway in diabetic complications (►**Figs. 6** and **7**).

"Disease–Drug Component–Target" Network Relationship Construction

Using Cytoscape 3.8.2 software, a "Disease–Drug Component–Target–Signal Pathway" network diagram was constructed. The network has a total of 713 nodes and 1,048 mutual relationships. Light green circles represent drugs; pink, red, purple, and orange hexagons represent active drug ingredients; dark green diamonds represent target sites; yellow hexagons represent shared components of Baimaogen (Imperatae Rhizoma) and Xiaoji (Cirsii Herba); and blue hexagons represent the SXD.

The analysis results showed that γ-aminobutyric acid had a degree value of 205, with a closeness centrality of 0.389283762; adenosine had a degree value of 155, with a

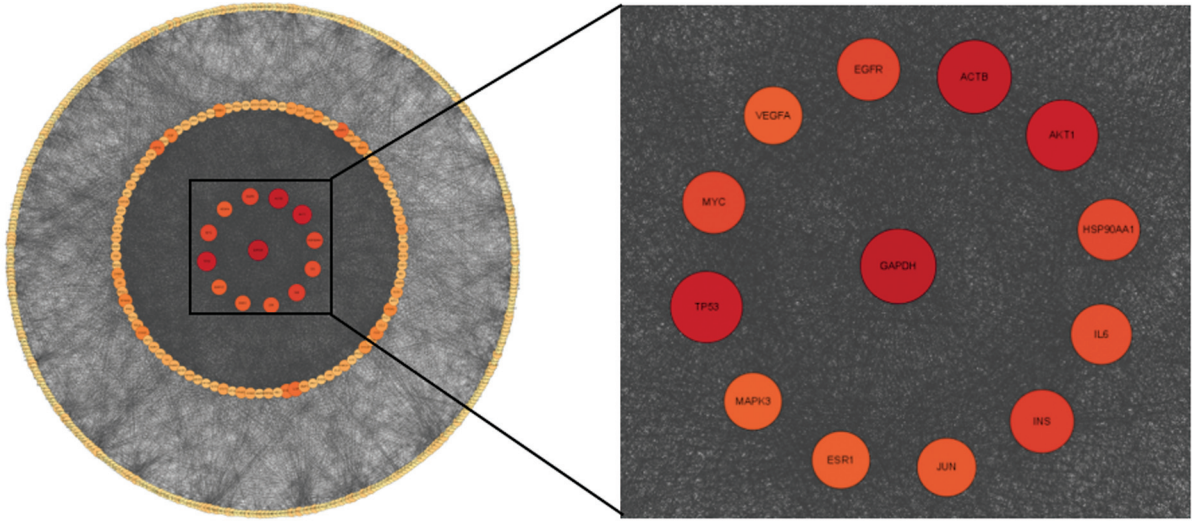


Fig. 2 Protein-protein interaction (PPI) network of common drug–disease intersection targets.

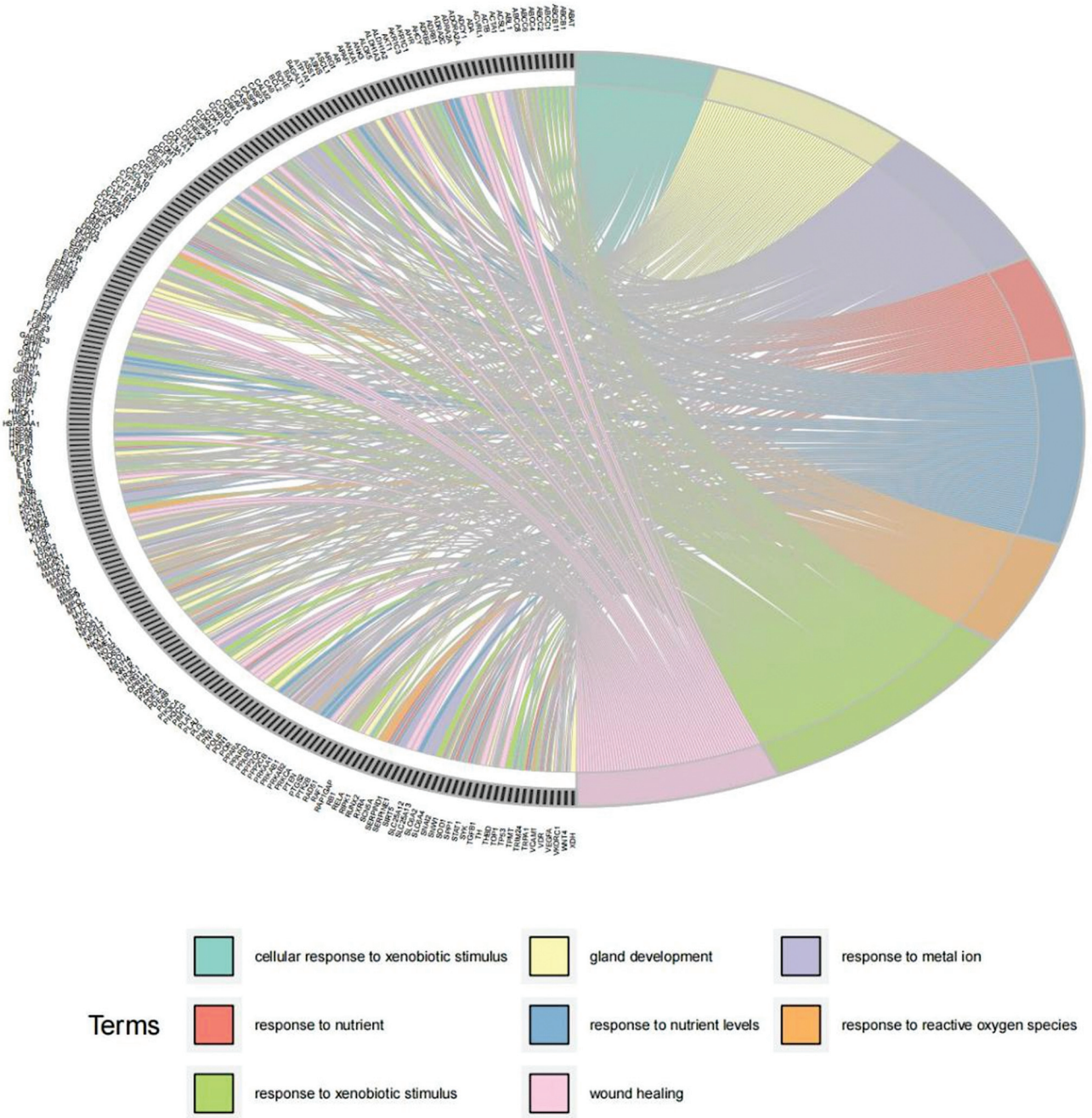


Fig. 3 Enrichment of top eight items in biological processes (BP) and related genes.

closeness centrality of 0.347486579; quercetin had a degree value of 139, with a closeness centrality of 0.381360471; taraxerol had a degree value of 54, with a closeness centrality of 0.304143528, etc. (►**Table 2** and ►**Fig. 8**).

Molecular Docking of Main Active Ingredients with Core Targets

The molecular docking results indicate that the core targets GAPDH, TP53, and ACTB have good binding affinity with the active ingredients adenosine and quercetin, with an affinity energy lower than $-5.0\,kJ{\cdot}mol^{-1}$. This suggests that the predicted results of the study are reliable (►**Table 3** and ►**Fig. 9**). GAPDH is the target with the highest degree value in the protein interaction network between the SXD and AML, and it is also a key enzyme involved in glycolysis. It has been found that glycolysis is a potential pathway for treating AML, and the glycolytic process in AML cells can effectively reduce the chemotherapy resistance of cytarabine.[10]

Discussion

AL can be classified within the scope of TCM as "acute exertion" and "heat exertion." In the early stages of AL, the initial symptoms often manifest as high fever similar to that of a cold, accompanied by chills, body aches, sore throat, and

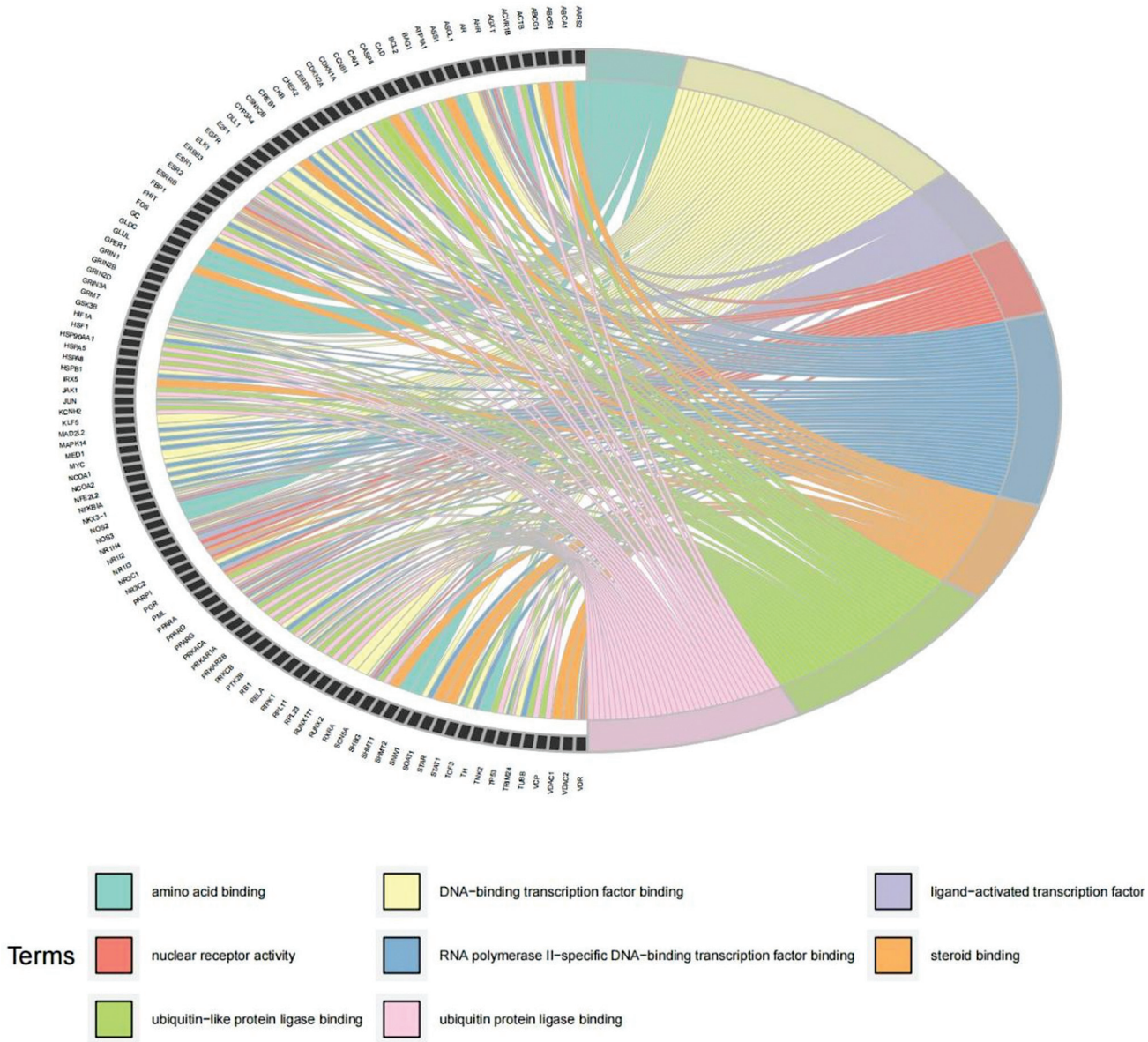


Fig. 4 Enrichment of top eight items in molecular functions (MF) and related genes.

other respiratory symptoms, all of which are consistent with the initial symptoms of a warm pathogen invasion. In the initial stage of AL, the manifestations are often high fever similar to that of a cold.[11] Studies have shown that multi-targeted therapy is more effective than single therapy. The SXD, as a classic prescription for treating AL in clinical practice, has strong prospects for basic research and clinical significance. However, the potential mechanism of the SXD in treating AL is not yet clear. This article uses network pharmacology for data mining and target prediction to explore the relationship between the components and predicted targets in the SXD and the relevant pathways of AL, providing a scientific basis for understanding the fundamental mechanism and clinical application of the SXD.

This study predicted a total of 30 active ingredients in the SXD, 677 potential drug targets, and 12,110 disease targets for AL, with a common target of 517 after taking the intersection of "drug–disease." KEGG analysis found that the SXD mainly exerts its anticancer cell proliferation, immune-boosting, and cell metabolism-regulating effects through the regulation of chemical carcinogen receptor activation, lipid and atherosclerosis, fluid shear stress and atherosclerosis, prostate cancer, and the AGE-RAGE signaling pathway in diabetic complications. Network topological analysis of the main active ingredients in the SXD showed that the components with higher degree values include γ-aminobutyric acid, adenosine, quercetin, taraxasterol, and scopolamine.

The top two listed above are both components of Shengdi (Rehmanniae Radix). Studies have found that γ-aminobutyric acid is involved in the proliferation, differentiation, and migration of various cancer cells, and through cell proliferation experiments using the MTT method, it has been confirmed to have a significant inhibitory effect on the

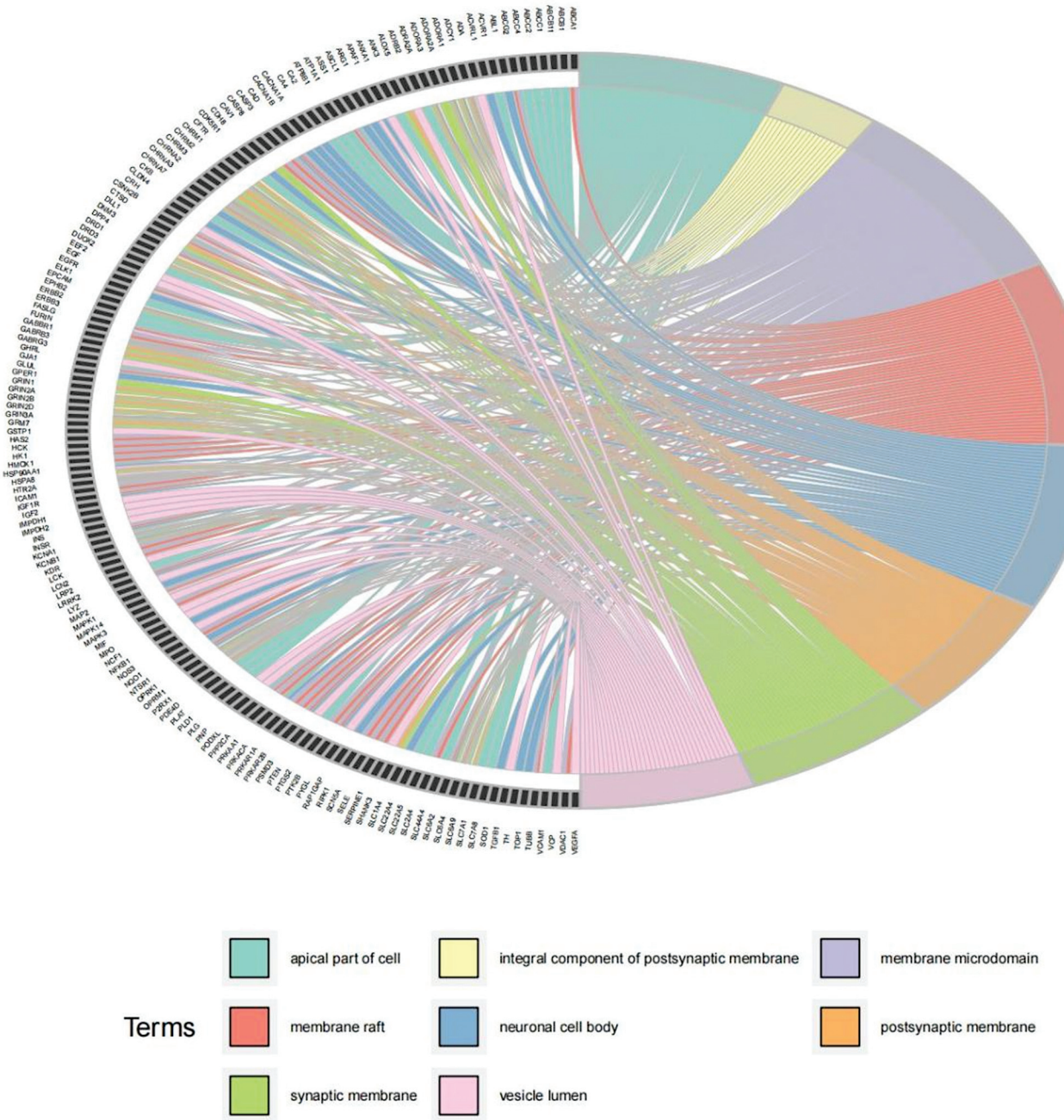


Fig. 5 Enrichment of top eight items in cellular components (CC) and related genes.

proliferation of HL-60 human acute promyelocytic leukemia cells.[12] Zhao et al[13] found that in the early stage of TCM "blood-activating" syndrome, a large intake of fresh Rehmanniae Radix juice can significantly reduce the expression of the tumor necrosis factor TNF-α in humans, thereby reducing the level of endotoxins in the blood, thus purifying the blood and protecting the gastrointestinal mucosal barrier.

Quercetin (Que) in Xiaoji (Cirsii Herba) ranks third in degree value and is a natural protective bioflavonoid. In recent years, multiple studies have confirmed that quercetin (Que) inhibits various tumor signal pathways, suppresses cancer cell proliferation, and effectively reduces the toxicity of certain chemotherapy drugs.[14] Chen et al[15] confirmed that Que can reduce the expression of HIF1α and VEGF in AML cell line U937, decrease the ratio of Bcl-2 to Bax, induce cell apoptosis, and inhibit U937 cell proliferation. Que significantly activates caspase-8, caspase-9, caspase-3, and PARP in human acute promyelocytic leukemia cell line HL-60, induces cell apoptosis, and markedly inhibits HL-60 cell proliferation.[16] Natural small thistle polysaccharides can promote the production of various cytokines such as tumor necrosis factor, interleukin, and interferon, significantly regulate immune function, and have anti-tumor effects.[17] Pharmacological studies have found that small thistle has significant pharmacological activities in hemostasis and coagulation,

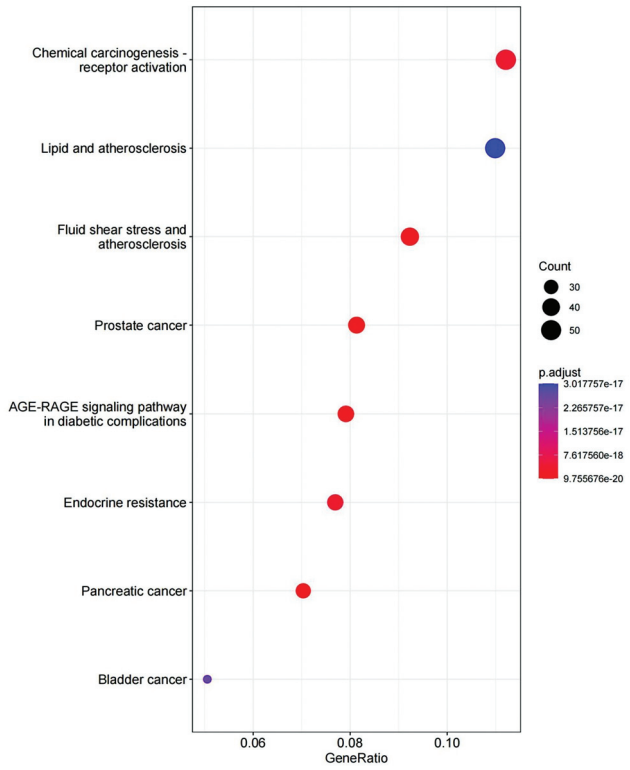


Fig. 6 Bubble chart of KEGG pathway enrichment analysis.

regulation of heart rate and blood pressure, regulation of glucose and lipid metabolism, anti-aging, anti-inflammatory and antibacterial effects, and bronchial smooth muscle contraction.[18]

Taraxerol is a pharmacological component of Pugongying (Taraxaci Herba) and belongs to the triterpenoid compound class. Taraxerol, one of the main triterpenoid compounds in dandelion, and its semisynthetic derivatives, can inhibit the proliferation of human acute promyelocytic leukemia cell line HL-60, chronic myeloid leukemia cell line K562, and acute T-cell lymphoblastic leukemia cell line Jurkat to varying degrees, without toxic side effects on normal peripheral blood cells. It is a natural antileukemia drug. Fresh Pugongying (Taraxaci Herba) has pharmacological effects such as antioxidant, blood glucose-lowering, anti-diabetic, antitumor, and anti-inflammatory properties. Ovadje et al[19] found that dandelion root extract can rapidly activate cell death receptor caspase-8 in Jurkat cells, a human acute T-cell lymphoblastic leukemia cell line, in a few minutes in an aqueous solution, followed by caspase-3 activation. This indicates that it can significantly induce exogenous and cell death receptor-mediated apoptosis of leukemia cells and exhibits time-concentration dependence, while having no impact on normal peripheral blood monocytes.

β-Sitosterol is derived from Baimaogen (Imperatae Rhizoma). Previous studies have shown that ß-sitosterol

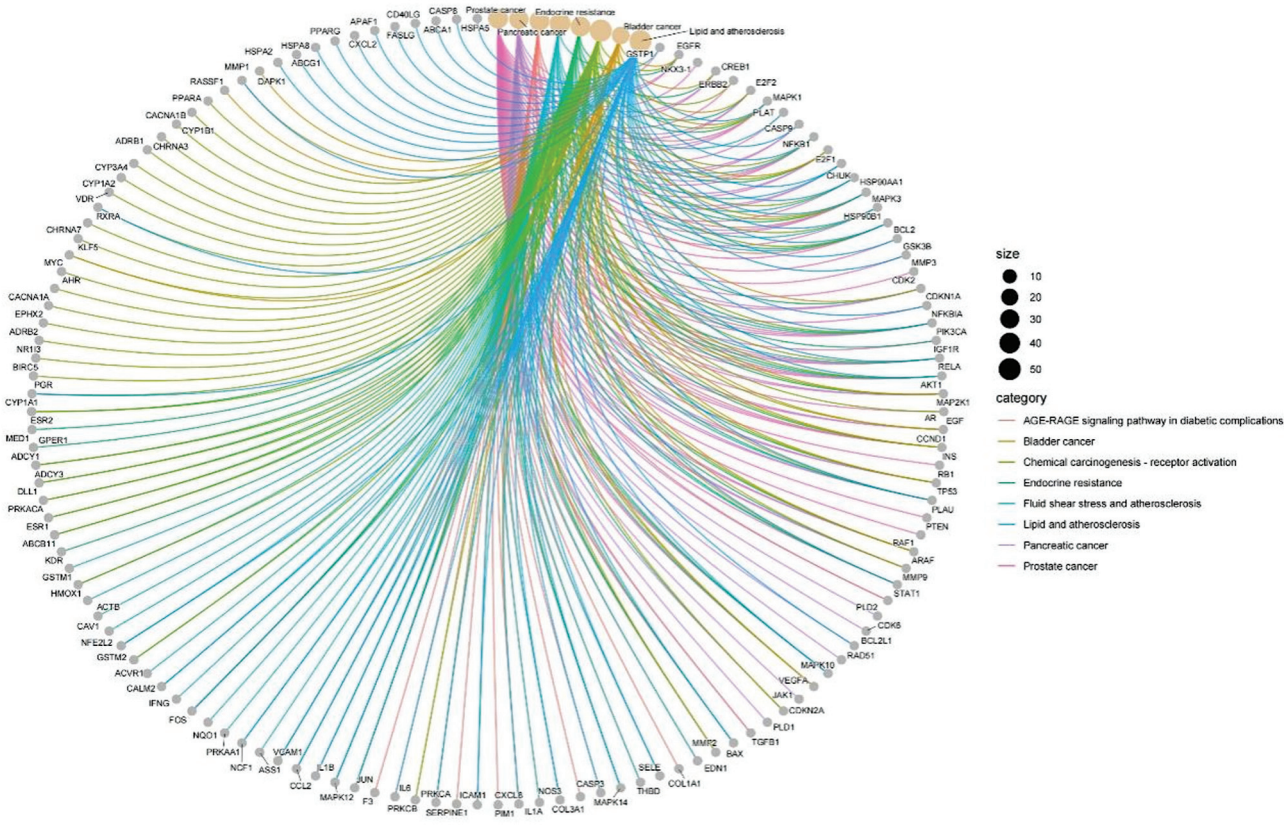


Fig. 7 Enrichment of top eight items in KEGG pathways and related genes.

Table 2 Network topology analysis of main active ingredients in the SXD (Top 10 degree values)

Chinese herbs	Active ingredients	Degree value	Closeness centrality
Shengdi (Rehmanniae Radix)	γ-aminobutyric acid	205	0.389283762
Shengdi (Rehmanniae Radix)	Adenosine	155	0.347486579
Xiaoji (Cirsii Herba)	Quercetin	139	0.381360471
Pugongying (Taraxaci Herba)	Taraxeryl	54	0.304143528
Xiaoji (Cirsii Herba)	Scopolamine	49	0.339532666
Baimaogen(Imperatae Rhizoma)	β-sitosterol	38	0.296790329
Pugongying (Taraxaci Herba)	Adenosine	37	0.259191846
Baimaogen(Imperatae Rhizoma)	elisabetta ferrero	37	0.252751154
Pugongying (Taraxaci Herba)	Choline	36	0.281311734
Baimaogen(Imperatae Rhizoma)	demecolcine	35	0.252392769

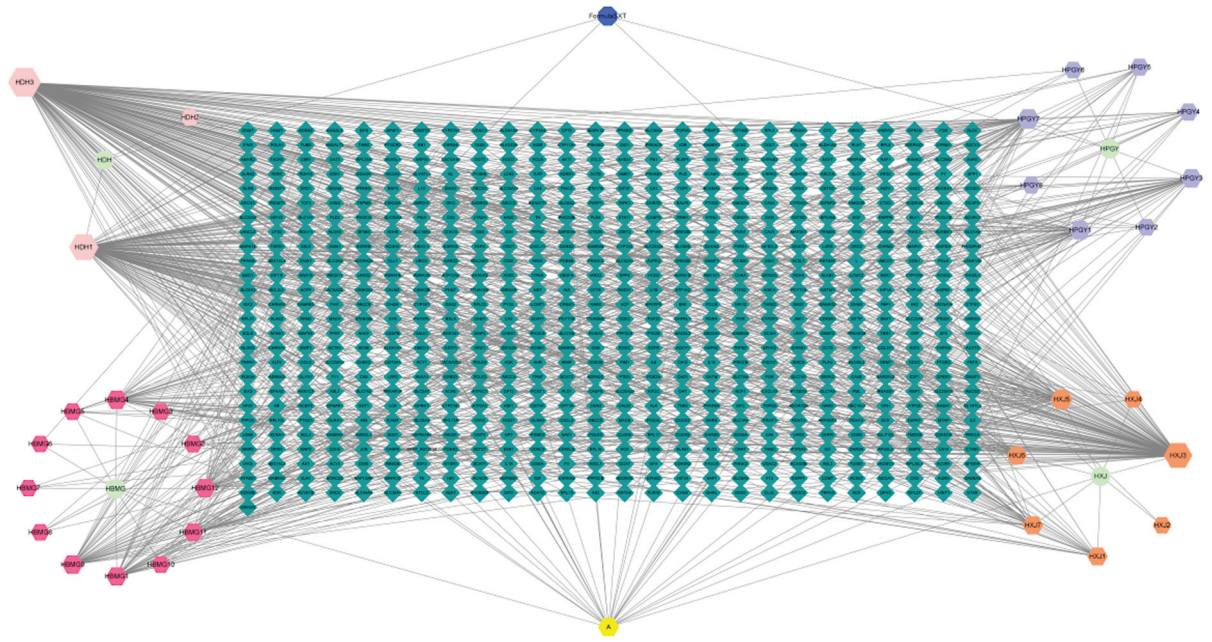
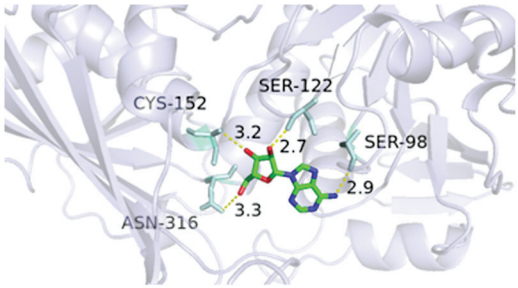


Fig. 8 Network diagram of "Disease-drug component-target".

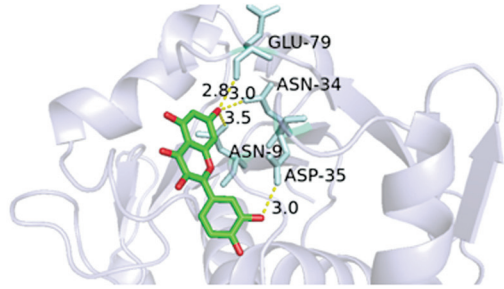
Table 3 Molecular docking binding energy information

No.	Chemical compound	Free binding energy (kJ·mol^{-1})		
		GAPDH	TP53	ACTB
1	Adenosine	−6.6	−5.1	−5.5
2	Quercetin	−6.1	−7.4	−6.3

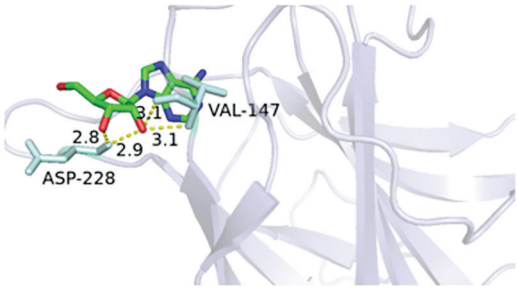
may block caspase-3 activation and PARP degradation by selectively inducing the Bax/Bcl-2 ratio, leading to proliferation and apoptosis of human AML cell line U937 cells.[20] White eulalia root also contains a significant amount of triterpenoid active ingredients.[21] Multiple studies have demonstrated that triterpenoid compounds can significantly increase the early apoptosis rate of acute monocytic leukemia cell line THP-1 and chronic myeloid leukemia cell line K562, block the cell cycle, and inhibit cell proliferation.[22,23] Baimaogen (Imperatae Rhizoma) was first recorded in the book *Sheng Nong's herbal classic (Shen Nong Ben Cao Jing)* and is described as having a sweet taste, cold nature, clearing heat-toxins, stopping bleeding and nourishing yin deficiency.



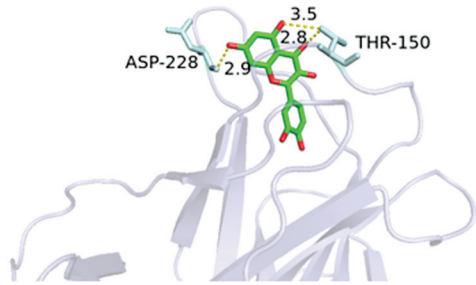
Adenine nucleoside-GAPDH（1U8F）



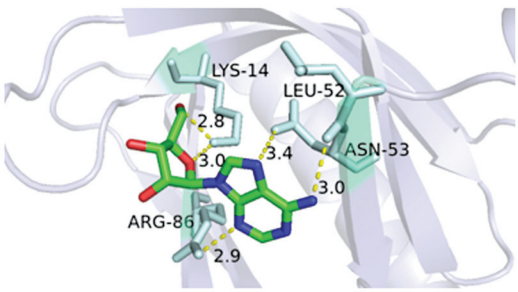
Quercetin-GAPDH（1U8F）



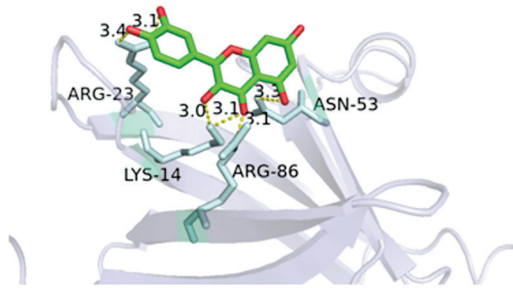
Adenine nucleoside-TP53（5O1H）



Quercetin-TP53（5O1H）



Adenine nucleoside-AKT1（1H10）



Quercetin-AKT1（1H10）

Fig. 9 Molecular docking of key components with core targets.

Conclusion

The SXD can play a therapeutic role in treating AL through its multiple components and targets. The main chemical components of the four fresh herbs that make up this formula can effectively inhibit leukemia cell proliferation and induce leukemia cell apoptosis. In order to accurately explore the mechanism of action of the SXD in treating AL, further animal or cell experiments are needed for verification to provide more solid and reliable scientific evidence.

CRediT Authorship Contribution Statement

Zihan Jiang: Date curation and formal analysis. Man Zhang: Methodology and validation. Jiayuan Guo: project administration and visualization. Jiayuan Guo: Resources. Wenqing Liu: Software. Jue Guo: Supervision. Qiuling Ma: Conceptualization, funding acquisition, writing—original draft, and writing—review & editing.

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Conflict of Interest

The authors declare no conflict of interest.

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