Hindawi
Journal of Chemistry
Volume 2024, Article ID 4309908, 13 pages
https://doi.org/10.1155/2024/4309908

Research Article

Identification of the Mechanism of Action of the Index Components of Banxia Xiexin Decoction for Gastric Cancer through Network Pharmacology, Bioinformatics, and Molecular Docking Analysis

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Received 29 October 2022; Revised 29 December 2023; Accepted 8 January 2024; Published 13 January 2024

Academic Editor: Barbara Gawdzik

Banxia Xiexin decoction (BXD) is a traditional prescription widely used to treat gastrointestinal conditions, including gastric cancer. Through network pharmacology, bioinformatics, and molecular docking analysis, this study aimed to investigate the potential mechanism of the antigastric cancer effect of BXD and pave the way for future research. The network pharmacology analysis used BXD index components to improve reliability and validity. Prognosis-related genes identified through Lasso and Cox regression analysis were considered potential BXD core targets for gastric cancer. Functional enrichment analysis was conducted to uncover the potential mechanism of action of BXD in gastric cancer. In addition, molecular docking of the index components of BXD and the core targets was used to validate the results. The present study obtained six index components of BXD and 155 corresponding antigastric cancer targets. ANXA5, CYP19A1, FGF1, and F2 in the prognostic signature model were identified as core targets of the index components of BXD. Protein-protein interaction networks and functional enrichment analysis indicated that proteoglycans in cancer, PI3K-Akt, and other pathways were involved. According to molecular docking results, six index components showed good-to-strong binding affinities to the core targets. The results indicated that the index components of BXD act on multiple pathways and targets of gastric cancer. Our study paved the way for further investigation of the antigastric cancer activity and mechanisms of BXD.

1. Introduction

Gastric cancer is one of the most prevalent and fatal diseases. More than one million new cases and 768,793 deaths from gastric cancer were reported worldwide in 2020. According to recent data, around 26,500 new cases of gastric cancer were diagnosed in the United States in 2023, resulting in approximately 11,130 deaths. Gastric cancer brings a great mental and economic burden to both patients and their families. The disease is becoming a social and economic burden for all countries, especially developing countries, including China [1–3]. Despite multiple therapeutic approaches such as surgical resection, chemotherapy, target therapies, and neoadjuvant chemoradiotherapy, the prognosis for patients with gastric cancer remains unsatisfactory [4, 5]. Therefore, it is imperative to identify and develop new approaches to treating gastric cancer.

BXD is composed of Rhizoma Pinelliae (Banxia in Chinese), Rhizoma Zingiberis (Ganjiang in Chinese), Radix Scutellariae (Huangqin in Chinese), Rhizoma Coptidis (Huanglian in Chinese), Radix Ginseng (Renshen in Chinese), Fructus Zizyphi Jujubae (Dazao in Chinese), and Radix Glycyrrhizae Preparata (Zhigancao in Chinese). The prescription has been used for thousands of years in China, Korea, and Japan to treat gastrointestinal disorders such as chronic gastritis, gastric ulcers, and dyspepsia [6]. The components of BXD, such as Radix Ginseng, play an important role in treating various diseases, including cancer and brain injury [7]. In recent decades, BXD has been used clinically to help gastric cancer patients manage their symptoms and extend their survival. The efficacy of BXD in gastric cancer has been evaluated in vivo and in vitro. BXD has been shown to inhibit tumor cell proliferation, halt the cell cycle, induce apoptosis, and boost treatment sensitivity in gastric cancer. However, the potential mechanism has not been fully elucidated [8, 9].

Network pharmacology is frequently used to explore the potential mechanisms of traditional Chinese medicine [10, 11]. We aimed to identify potential targets of BXD and uncover the antigastric cancer mechanism of BXD through network pharmacology, bioinformatics, and molecular docking analysis. In contrast to prior research, we focused on the index component of BXD acquired from an HPLC-based study [12]. We employed the least absolute shrinkage and selection operator (Lasso) and Cox regression analysis to identify potential core targets, thereby enhancing the reliability and validity of our work. The present study provides new insight into the mechanism of BXD in treating gastric cancer. The flowchart for this work is depicted in Figure 1.

2. Materials and Methods

2.1. Characterization of BXD Components and Comprehensive ADMET and Drug-Likeness Assessment. A recent analysis of the fingerprint spectrum and index components of BXD using HPLC identified seven index components [12]. The chemical structures in SDF format and SMILES strings of the index components were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [13]. The SwissADME tool (https://www.swissadme.ch/) was applied, based on six rules, including Lipinski, Ghose, Veber, Egan, and Muegge, and a bioavailability score was applied to assess the drug-likeness of the index components [14]. The bioavailability score was removed from the list of criteria, as it does not offer a definitive standard for drug-likeness compared to the other rules provided by the SwissADME tool. To assess index components' potential efficacy and safety in gastric cancer treatment, we comprehensively evaluated their ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. The analysis was performed using the pkCSM web-based platform [15]. The potential of the compounds for effective oral administration was assessed through their extent of intestinal absorption. Their metabolism was assessed by analyzing interactions with key cytochrome P450 enzymes, specifically CYP3A4 and CYP2D6. Toxicity profiles, including hepatotoxicity and genotoxicity (AMES toxicity), were evaluated to predict adverse effects. Total clearance rates were examined to understand the compounds' elimination from the body, which influences dosage and frequency considerations.

2.2. Targets of the Index Components of BXD. An extensive library of pharmacophores, including TargetBank, DrugBank, and BindingDB, supports the PharmMapper database (https://lilab-ecust.cn/pharmmapper/index.html) that was employed to obtain the targets of the index components of BXD [16]. SDF-format chemical structures were entered into the website's query file, with a maximum number of 300 generated conformations. Meanwhile, the target was selected as "human protein targets only," and the maximum number of 1000 reserved matches was set to 1000.

2.3. Screening of Targets of Index Components of BXD against Gastric Cancer. Genes associated with gastric cancer have been identified through various databases using "gastric cancer" as a keyword. Scores greater than 10 and 0.1 were defined as screening criteria in the GeneCards (https://www.genecards.org/) and DisGeNET (https://www.disgenet.org/) databases, respectively [17, 18]. The mapping of targets to diseases with ICD identifiers and UniProt IDs for all targets was downloaded from the Therapeutic Target Database (TTD, https://db.idrblab.net/ttd/) [19]. Gastric cancer-related targets were obtained after eliminating duplicate values from different databases. The intersection of the targets of the index components and gastric cancer-related targets was obtained with a Venn diagram using the Xiantao Academic tool (https://www.xiantao.love/), which is embedded with R (Version 3.6.3) and R packages [20].

2.4. Identification of Core Targets of BXD Index Components. RNA-sequencing expression files (level 3) of gastric cancer patients and corresponding clinical data were obtained from The Cancer Genome Atlas (TCGA; https://portal.gdc.com) database. The Lasso regression algorithm with 10-fold cross-validation was used to construct a prognostic signature. Log-rank tests and univariate Cox proportional hazards regression calculated the hazard ratio (HR) with a 95% confidence interval (CI) and p value. Core target expression and survival analysis heat maps were visualized with Xiantao Academic. Potential core targets of the index components of BXD for gastric cancer were identified by examining prognosis-related genes within the prognostic signature.

2.5. Protein-Protein Interaction (PPI) Network Construction and Clustering Analysis. The STRING database [21] (https://www.string-db.org/, Version 11.5) and Cytoscape (Version 3.9.1) software [22] were used to build the PPI network. Potential targets were imported into the STRING database with the "homo sapiens" setting and the highest confidence interaction score of 0.9. The result was exported in TSV format and then imported into Cytoscape. The network

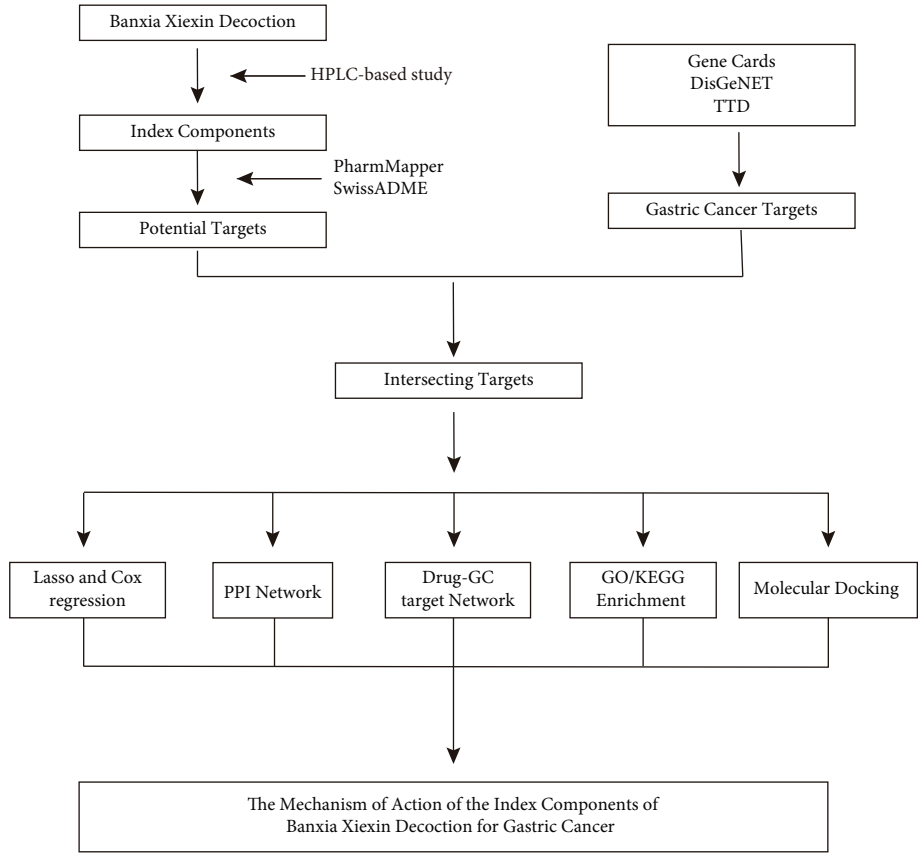


Figure 1: Flowchart of the present work. BXD index components acquired from an HPLC-based study were used in the network pharmacology analysis. Lasso and Cox regression analyses were employed to identify prognosis-related genes and potential BXD core targets for gastric cancer. PPI network and GO/KEGG enrichment analysis were conducted to uncover the potential mechanism of action of BXD in gastric cancer. In addition, molecular docking was employed to validate the results by examining the interactions between the index components of BXD and the core targets.

analyzer in Cytoscape was used to calculate the degree values of nodes. Cluster analysis was then conducted using the Molecular Complex Detection (MCODE) plugin [23] (Version 2.0.2) with the degree cutoff set to 2, the node score cutoff set to 0.2, the K-core set to 2, and the maximum depth set to 100.

2.6. Index Components-Gastric Cancer Targets Network Construction. To explore the potential mechanism of index components of BXD in treating gastric cancer, we constructed an index component-gastric cancer target network with Cytoscape.

2.7. GO/KEGG Enrichment Analysis. Xiantao Academic is a database embedded with R and R packages for data analysis and visualization. Gene ontology (GO)/Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed using Xiantao Academic. Terms with a p value of less than 0.05 and a false discovery rate (FDR) adjustment below 0.2 were deemed statistically significant. The most significantly enriched results were presented using bubble charts from Xiantao Academic.

2.8. Molecular Docking. Molecular docking simulation was applied using AutoDock Vina [24] (Version 1.2.0) to validate the binding of index components to predicted core targets according to the tutorial (https://autodock-vina.readthedocs.io/en/latest/index.html). Binding affinities of −4.25 kcal/mol, −5.0 kcal/mol, and −7.0 kcal/mol were classified as standard, good, and strong, respectively [25]. As binding energies decrease, the effectiveness of the binding mode increases.

3. Results

3.1. ADMET and Drug-Likeness Assessment of BXD Index Components. The present study focused on the potential therapeutic effect of the index components of BXD against gastric cancer. A recent study identified seven phytochemicals as the fingerprint spectra and index components of BXD based on HPLC [12]. Epiberberine, coptisine, and palmatine account for 1.06%–2.40% of BXD, whereas berberine accounts for 1.96%–4.12%, baicalin 8.48%–10.12%, glycyrrhizic acid 1.23%–2.05%, and 6-gingerol 0.18%–0.24%. The phytochemicals' chemical structures and SMILES strings were obtained from the PubChem database. In the

study, Figure 2 displays the 2D structure of the BXD index components, while Table 1 illustrates the results of the in silico ADMET properties and drug-likeness assessment of these components. A comprehensive overview of the ADMET profiles of all compounds is provided in Supplementary File S1. Glycyrrhizic acid did not meet any of the drug-likeness criteria, so it was excluded from further investigation.

3.2. Screening of Targets of the Index Components of BXD in Gastric Cancer. Potential targets of the six index components were predicted using the PharmMapper database, and 434 targets were obtained. A total of 1114, 364, and 75 relevant targets were acquired from the GeneCards, DisGeNET, and TTD databases, respectively. After deleting duplicate results, 1344 targets were obtained. A Venn diagram was constructed and 155 intersected targets were considered potential targets of the six BXD index components for treating gastric cancer (Figure 3).

3.3. Identification of Core Targets of BXD Index Components. Figures 4(a) and 4(b) show that Annexin A5 (ANXA5), cytochrome P450 family 19 subfamily A member 1 (CYP19A1), fibroblast growth factor 1 (FGF1), and coagulation factor II (F2) were linked to the prognosis of patients with gastric cancer in the model. Samples were divided into groups according to risk scores calculated from ANXA5, CYP19A1, FGF1, and F2 expression data (Figure 4(c)). The Kaplan–Meier analysis shows that patients with higher risk scores had a worse prognosis (Figure 4(d)). A universal Cox regression analysis showed ANXA5, CYP19A1, FGF1, and F2, and the risk score were correlated to the prognosis of gastric cancer (Figure 4(e)). The nomogram shows the prognostic signature for the gastric cancer nomogram (Figure 4(f)).

3.4. PPI Analysis of Common Targets. To explore the relationship between the targets of the index components of BXD for gastric cancer, a PPI network with 133 nodes and 595 edges was constructed with the STRING database and the Cytoscape software (Figure 5(a)). Six clusters were obtained using the MCODE plugin. The first cluster comprised 15 nodes and 66 edges, scoring 9.429. (Figure 5(b)). The seed node of the first cluster was insulin-like growth factor I (IGF1), which promotes cell growth and plays an important role in multiple pathways including the PI3K-AKT/PKB and Ras-MAPK pathways. The second cluster had 15 nodes and 37 edges, with a score of 5.286 (Figure 5(c)). Cell division control protein 42 homolog (CDC42) was the seed node of the second cluster. It regulates cellular responses, epithelial cell polarization, bipolar attachment of spindle microtubules to kinetochores, and cell migration. The third cluster comprised 5 nodes and 9 edges, scoring 4.500 (Figure 5(d)). Matrix metalloproteinase-3 (MMP3) was the seed node of the third cluster. It breaks down the extracellular matrix and promotes cancer metastasis. The fourth cluster had 13 nodes and 23 edges, with a score of 3.833 (Figure 5(e)). This cluster was seeded by retinoic acid receptor alpha (RARA), which regulates clock gene transcription, differentiation, and apoptosis. The fifth and sixth clusters both had three nodes and three edges, with a score of 3.000 (Figures 5(f) and 5(g)). Aldo-keto reductase family 1 member C3 (AKR1C3), which may regulate cell growth and/or differentiation, was the seed of the fifth cluster. Meanwhile, cathepsin B (CTSB), which contributes to tumor invasion and metastasis, was the seed of the sixth cluster. Figure 5(h) shows the scores of different clusters.

3.5. Index Components-Gastric Cancer Targets Network Construction. An index component-gastric cancer targets network consisting of 161 nodes and 672 edges was constructed (Figure 6(a)). All index components were related to multiple targets. The average number of targets and the degree of the index components were 113.8. Among the six index components, baicalin had the most targets (degree = 153), followed by 6-gingerol (degree = 141), palmatine (degree = 100), epiberberine (degree = 98), berberine (degree = 93), and coptisine (degree = 87) (Figure 6(b)).

3.6. GO/KEGG Enrichment Analysis. This study utilized GO and KEGG enrichment analyses to explore the potential synergistic mechanisms of index components of BXD for gastric cancer. GO enrichment includes terms such as biological process (BP), cellular component (CC), and molecular function (MF). The targets were enriched in 2081 GO-BP terms, 55 GO-CC terms, 172 GO-MF terms, and 139 KEGG pathways (Supplementary Files S2–S5). The top 10 terms enriched by GO-BP, -CC, and -MF are shown in Figures 7(a)–7(c). The top 5 terms enriched for GO-BP were gland development (GO: 0048732), response to reactive oxygen species response (GO: 0000302), protein kinase B signaling (GO: 0043491), cell response to oxidative stress (GO: 0034599), and reproductive structure development (GO: 0048608). The top 5 GO-CC terms enriched were ficolin-1-rich granule (GO: 0101002), ficolin-1-rich granule lumen (GO: 1904813), vesicle lumen (GO: 0031983), secretory granule lumen (GO: 0034774), and cytoplasmic vesicle lumen (GO: 0060205). The top 5 terms enriched by GO-MF were protein tyrosine kinase activity (GO: 0004713), nuclear receptor activity (GO: 0004879), transcription factor activity, direct ligand regulated sequence-specific DNA binding (GO: 0098531), steroid hormone receptor activity (GO: 0003707), and transmembrane receptor protein kinase activity (GO: 0019199).

KEGG enrichment analysis enabled us to identify signaling pathways associated with targets of the index components of BXD. In the present study, 155 potential targets were enriched in 139 KEGG pathways. The top 10 pathways enriched involved proteoglycans in cancer (hsa05205), prostate cancer (hsa05215), PI3K-Akt signaling (hsa04151), resistance to EGFR tyrosine kinase inhibitor (hsa01521), endocrine resistance (hsa01522), Ras signaling (hsa04014), MAPK signaling (hsa04010), FoxO signaling (hsa04068), estrogen signaling (hsa04915), and Rap1 signaling (hsa04015) (Figure 7(d)). Approximately 38 out of 155

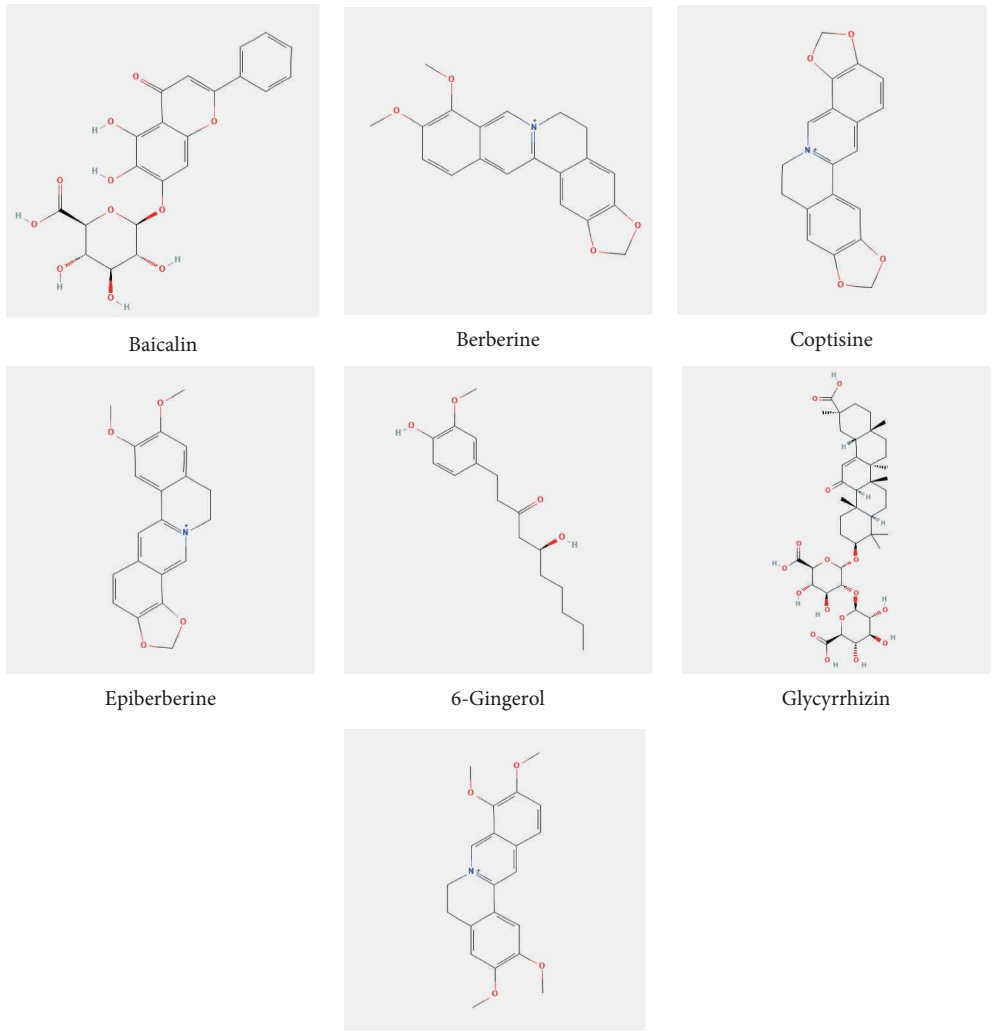


Figure 2: Two-dimensional (2D) configuration of BXD's index components as derived from the PubChem database.

Table 1: The in silico ADMET properties and drug-likeness assessment of the index components of BXD.

Phytochemicals	ADMET properties					Drug-likeness rules				
	Intestinal absorption (%)	CYP2D6/CYP3A4 substrate	Total clearance (log ml/min/kg)	AMES toxicity	Hepatotoxicity	Lipinski	Ghose	Veber	Egan	Muegge
Baicalin	26.224	No	0.04	No	No	No	Yes	No	No	No
Berberine	97.147	Yes	1.27	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Coptisine	98.07	Yes	1.28	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Epiberberine	97.961	Yes	1.278	No	Yes	Yes	Yes	Yes	Yes	Yes
Palmatine	97.084	Yes	1.246	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glycyrrhizic acid	0	Yes	−0.304	No	No	No	No	No	No	No
6-Gingerol	92.416	No	1.339	No	No	Yes	Yes	Yes	Yes	Yes

potential targets of the index components of BXD were enriched in the PI3K-Akt signaling pathway, which regulates many basic cell processes, including cell growth, transcription, translation, cell proliferation, cell movement, and glycogen metabolism.

3.7. Molecular Docking Simulation. Antigastric cancer core targets were molecularly docked with six BXD index components using AutoDock Vina. The molecular docking setting is presented in Supplementary File S6, and the details of the results are presented in Table 2. The representative

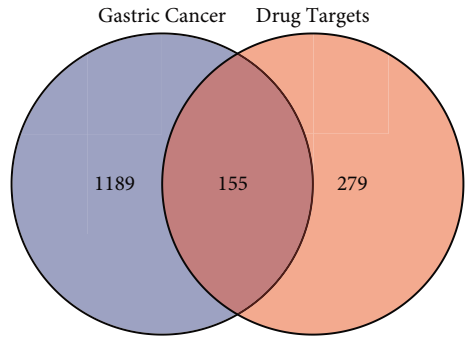


Figure 3: The Venn diagram shows the intersection of gastric cancer-relevant targets and the predicted targets of the index components of BXD.

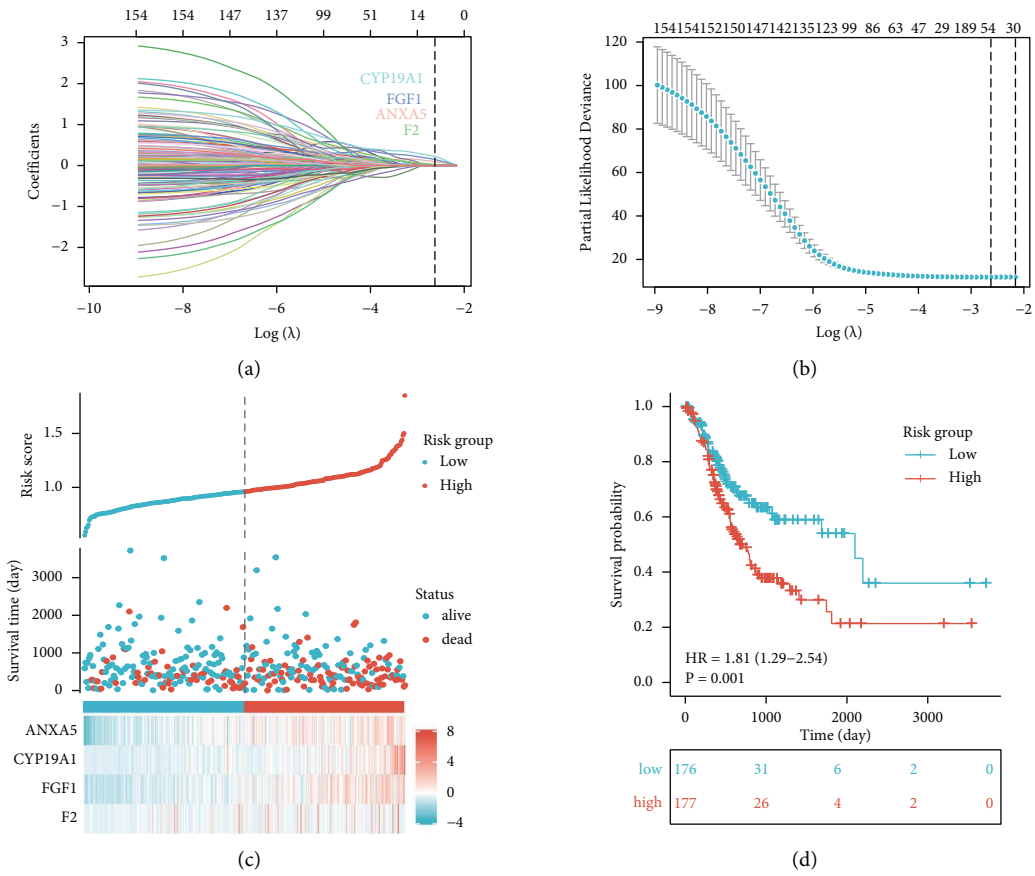
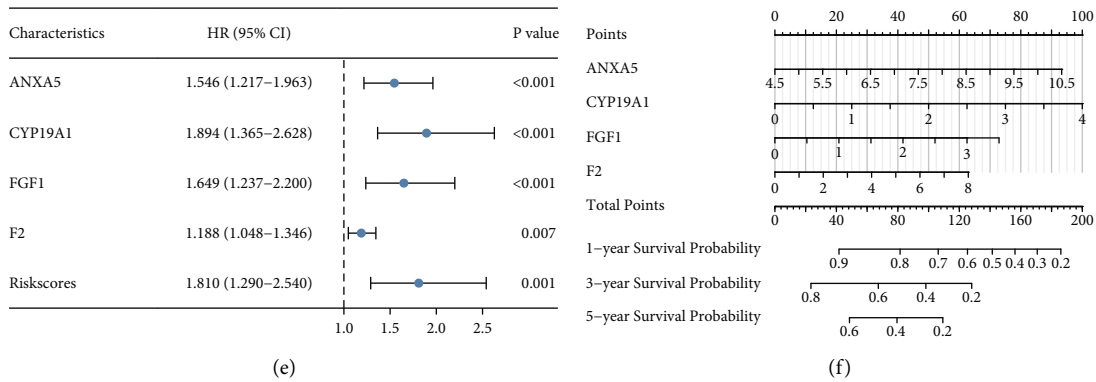
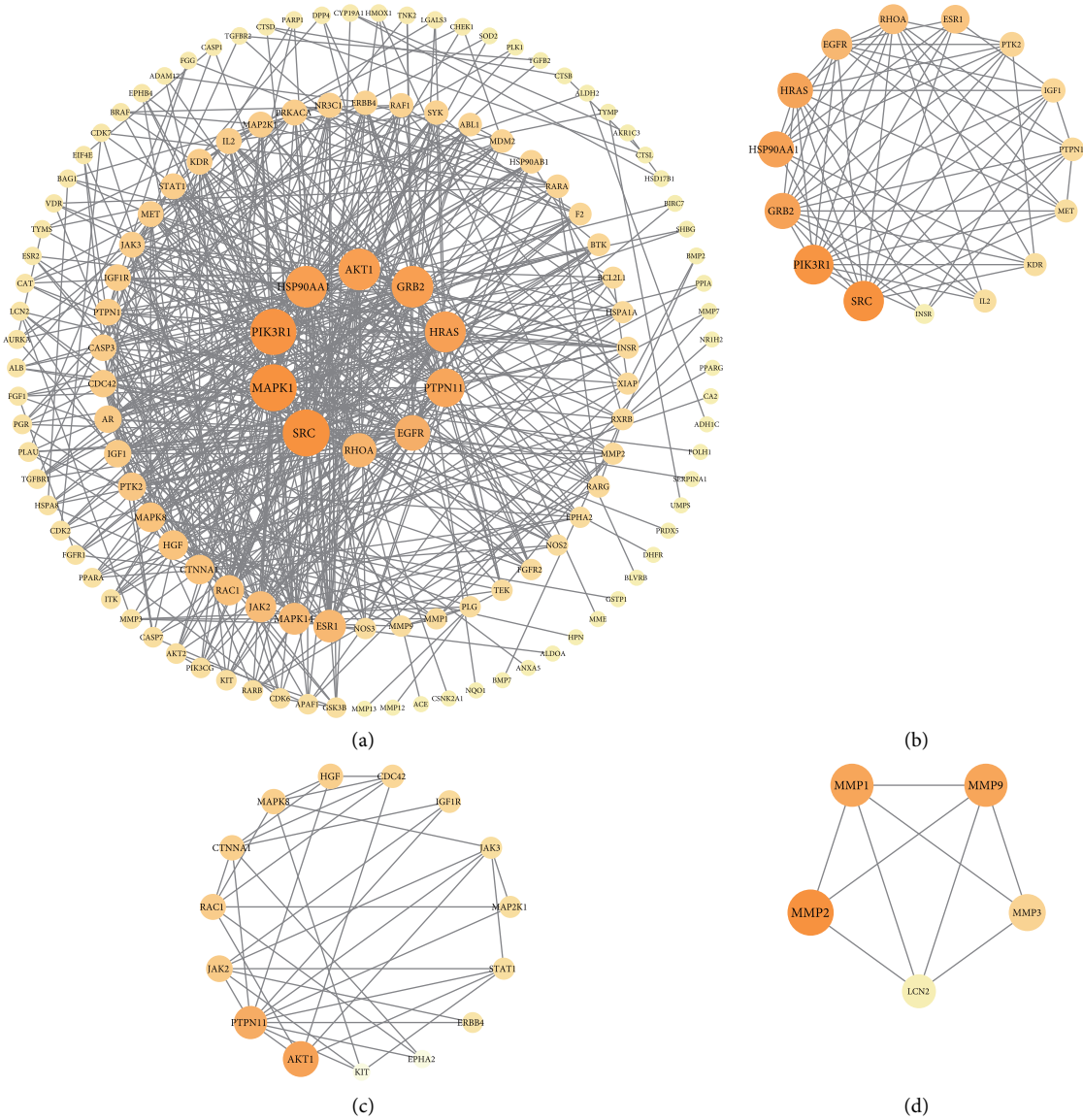


Figure 4: Continued.



(e) (f)

FIGURE 4: Lasso regression analysis identified four genes related to the prognosis of gastric cancer patients. (a–b) Lasso prognostic regression model. Relationship of potential target coefficients, partial likelihood deviation, and log(λ) in the model. The smaller the likelihood deviation, the better the corresponding model. Four features (targets) remained in the model (the first vertical dotted line from left to right). (c) Risk scores for gastric cancer samples are shown as a scatter plot, together with the survival time and survival status (samples were divided into two groups by median). Expression levels of targets in the prediction model were shown with heatmap. (d) Kaplan–Meier survival analysis of the risk model. (e) Forest plot of Cox regression results. (f) Nomogram shows the prognostic signature for gastric cancer.



(a) (b) (c) (d)

FIGURE 5: Continued.

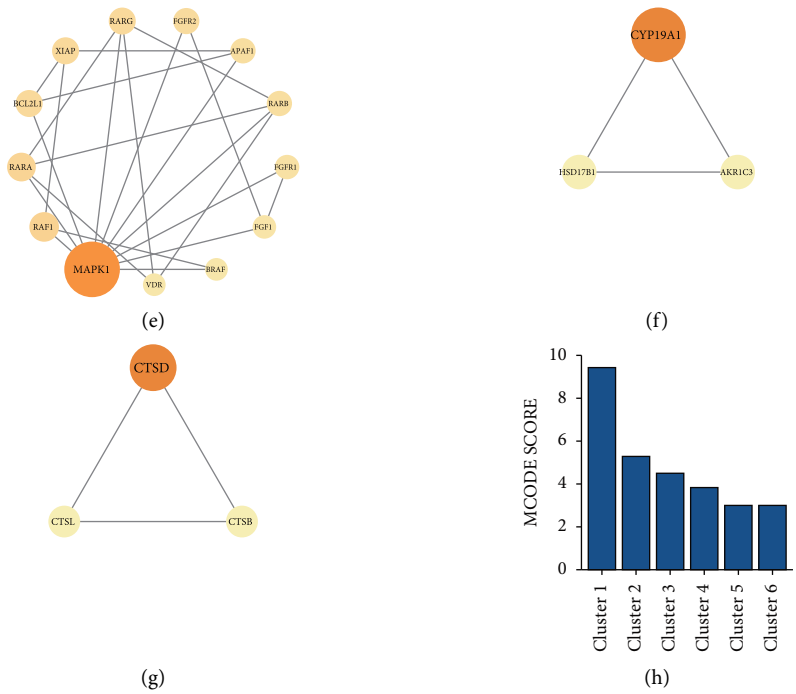


Figure 5: Protein-protein interaction analysis of the targets of the index components of BXD in gastric cancer treatment. (a) The whole PPI network of the targets. The analysis of the PPI network identified 10 core targets of the index components in gastric cancer treatment. (b–g) Cluster analysis using MCODE in Cytoscape identified six clusters. (h) The MCODE score of different clusters. The greater the value, the greater the node's significance, size, and darkness.

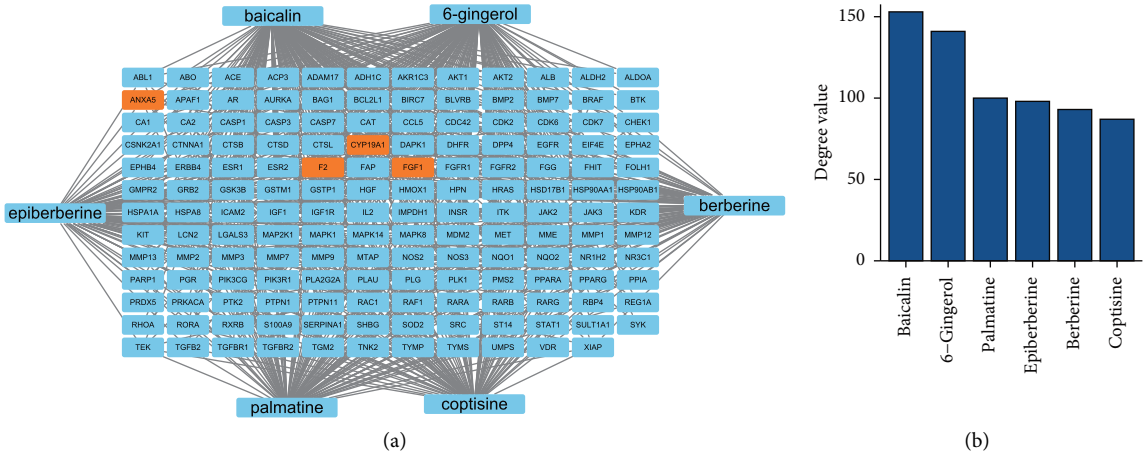


Figure 6: The index components-gastric cancer targets network. (a) Network construction. The core targets identified using Lasso regression analysis are highlighted in orange. (b) The degree values of each index component.

docking results are presented in Figure 8. The results of the docking analysis suggest that berberine interacts with CYP19A1 through a carbon-hydrogen bond, pi-alkyl, and pi-donor hydrogen bonds. These interactions are responsible for the strong binding affinity of −11.2 kcal/mol, which indicates a potent interaction with potential pharmacological importance.

Similarly, the binding between coptisine and CYP19A1 involves a combination of carbon-hydrogen bond, pi-alkyl, amide-pi stacked, and pi-sulfur interactions, indicating

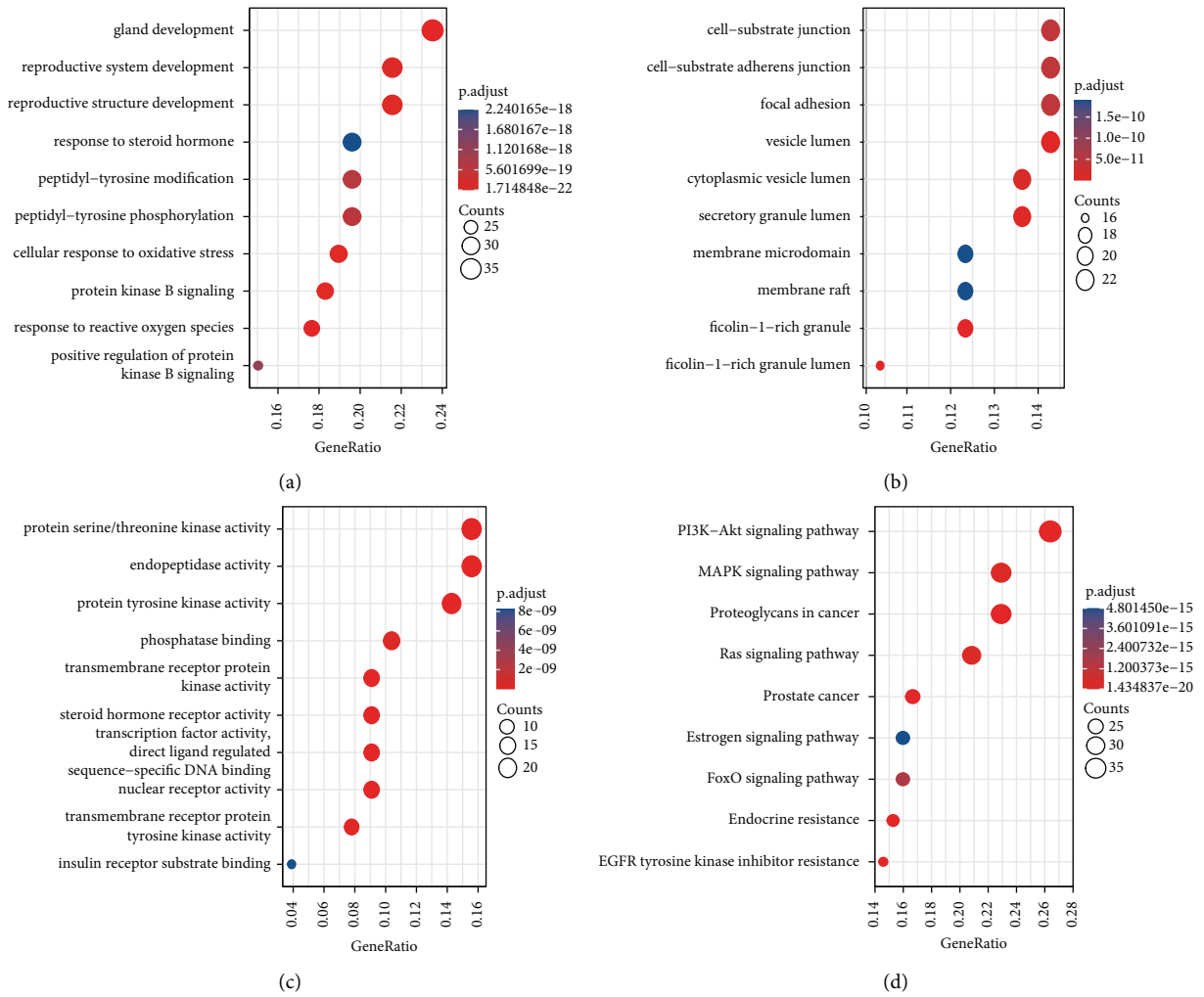


Figure 7: GO/KEGG analysis of the 155 targets. (a–c) Top 10 enriched GO BP, CC, and MF terms. (d) Top 10 enriched KEGG pathways involved in the index components of BXD in gastric cancer treatment. Colors represent the significance of differential enrichment, the size of the bubble represents the number of targets, and the larger the bubble, the greater the number of targets. Adjusted p value <0.05 is considered to be significantly different.

Table 2: Molecular docking of core targets with the index components of BXD (kcal/mol).

Targets	Baicalin	Berberine	Coptisine	Epiberberine	Palmatine	6-Gingerol
ANXA5	−10.0	−10.1	−11.0	−10.3	−9.2	−7.3
CYP19A1	−10.1	−11.2	−11.1	−9.9	−9.0	−7.3
FGF1	−10.3	−9.1	−10.1	−9.0	−8.4	−6.3
F2	−8.5	−7.6	−9.3	−8.2	−9.0	−7.3

a robust interaction with the target that may influence its biological activity. The interaction between ANXA5 and coptisine is characterized by a carbon-hydrogen, pi-alkyl, and pi-donor hydrogen bonds, suggesting a stable binding mechanism relevant to the compound's therapeutic potential.

4. Discussion

Originating from the esteemed Treatise on Febrile Diseases (known as Shanghan Lun in Chinese), BXD stands as a time-honored prescription that has gained widespread acceptance for its efficacy in treating gastrointestinal disorders,

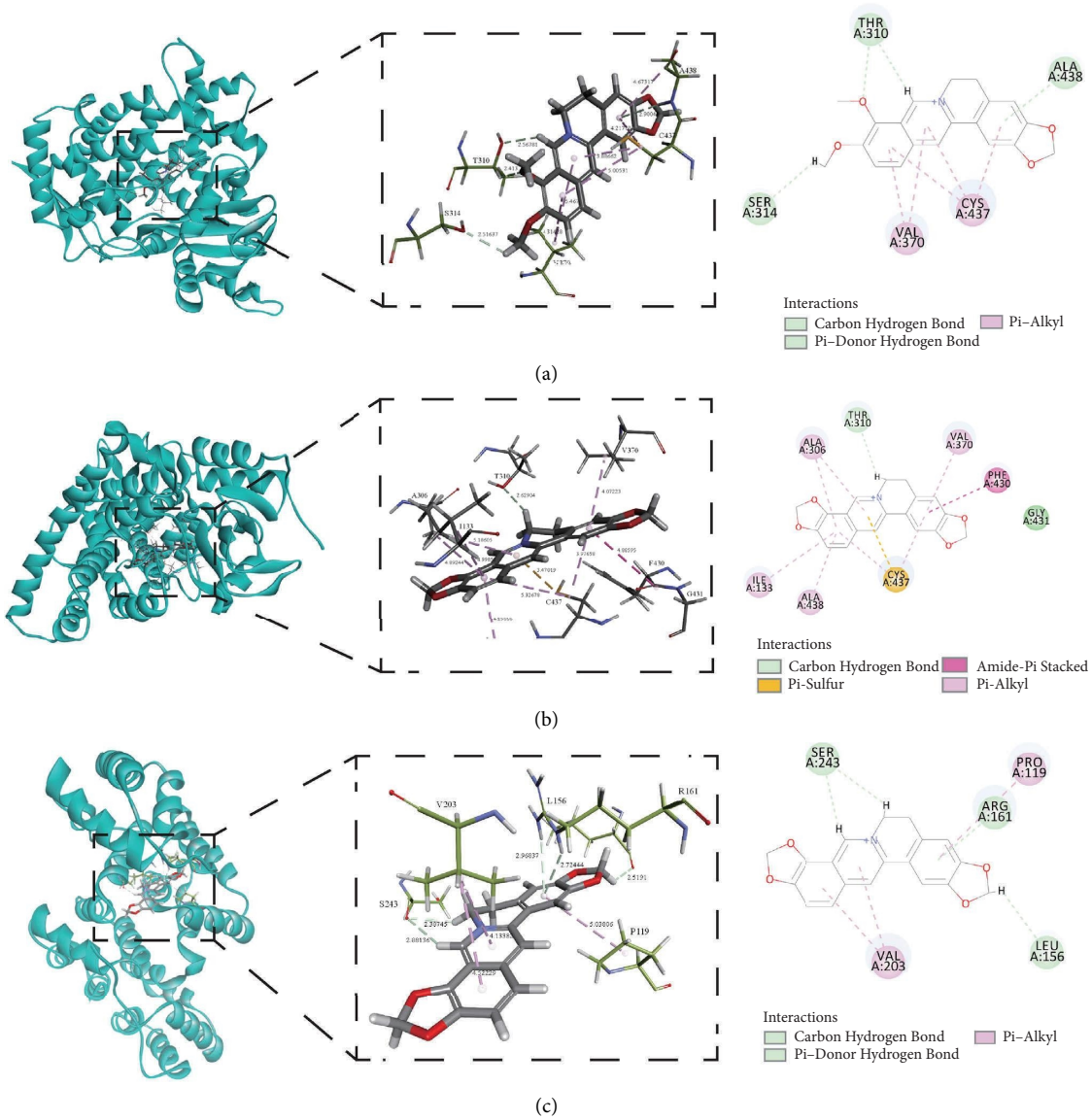


Figure 8: Schematic diagram of the docking results. The ligands bind to the receptor through various forces. (a) CYP19A1 and berberine. (b) CYP19A1 and coptisine. (c) ANXA5 and coptisine.

including chronic atrophic gastritis, gastric ulcer, dyspepsia, and gastric cancer [26]. However, the potential mechanisms underlying the action of BXD in the treatment of gastric cancer remain elusive. The present study comprehensively investigated the potential mechanisms of BXD for gastric cancer through network pharmacology, bioinformatics, and molecular docking analysis.

In many studies involving network pharmacology analysis, the amounts of the compounds in the preparation or plant have not been considered, leading to nonspecific components and targets [27]. Consequently, the index components of BXD obtained from a recent HPLC-based study [12] were used in our study to evaluate the antigastric cancer effect of BXD. Furthermore, we developed a clinical prediction model utilizing potential targets of BXD, instead of relying on the degree value of targets within the protein-protein interaction network to identify core targets. This approach strengthened the credibility and quality of our study. This study included six of the seven index components of BXD after undergoing drug-likeness assessment, and 155 corresponding targets for gastric cancer were identified. The network analysis of index components and targets demonstrated that baicalin, berberine, coptisine, epiberberine, palmatine, and 6-gingerol collaboratively influence gastric cancer by acting on multiple targets. Four primary targets, ANXA5, CYP19A1, FGF1, and F2, were particularly significant in this process.

ANXA5 has been linked to unfavorable outcomes in gastric cancer cases [28]. Despite these correlations, experimental evidence delineating ANXA5's functional role in gastric cancer remains elusive, highlighting the need for rigorous investigations on ANXA5's mechanistic involvement in gastric carcinogenesis. Such research could shed light on its potential as a therapeutic target for Banxia

Xiexin decoction. CYP19A1 catalyzes the synthesis of steroids, which are involved in the development of gastric cancer [29]. Based on immunohistochemistry findings, CYP19A1 has been reported to be upregulated in gastric cancer tissues, and it has been suggested as an independent biomarker for gastric cancer [30]. Phytomedicines that induce downregulated CYP19A1, such as ursolic acid and taxifolin, reduce the malignancy and progression of gastric cancer [31, 32]. Previous research showed that FGF1 overexpression promoted metastasis, invasion, and differentiation of gastric cancer and was correlated with poor prognosis [33]. Another study discovered that FGF1 downregulation inhibited angiogenesis in the xenograft mouse model [34]. F2, also known as coagulation factor II and thrombin, is essential for cell proliferation, tissue repair, and angiogenesis. Evidence showed that F2 was responsible for epithelial-mesenchymal transition (EMT) in gastric cancer [35]. Our study used Lasso regression analysis with ten-fold cross-validation and built a prognostic signature for gastric cancer. The signature comprised ANXA5, CYP19A1, FGF1, and F2, regarded as the core targets of the index components of BXD in treating gastric cancer. Patients with higher risk scores have a worse prognosis. The molecular docking study results showed specific interactions between CYP19A1 and berberine, with a strong binding affinity of −11.2 kcal/mol. These interactions suggest that the components of BXD have potential inhibitory effects on the targets and may help treat cancer. This new information is invaluable for predicting the effectiveness and specificity of these compounds in future therapeutic applications. Further experiments are required to examine this issue.

GO/KEGG enrichment showed that proteoglycans in cancer, the PI3K-Akt signaling pathway, EGFR tyrosine kinase inhibitors, and the Ras and MAPK signaling pathways were potential antigastric cancer mechanisms of BXD. Proteoglycans are essential in cancer progression directly and through their interactions with other molecules, including growth factors and cytokines. Some proteoglycans function as tumor suppressors [36]. Recent evidence from a cohort study suggested that overexpression of extracellular proteoglycan biglycan may serve as a possible prognostic biomarker and therapeutic option for patients with advanced gastric cancer [37]. Proliferation, metastasis, and chemoresistance in gastric cancer may all result from abnormal activation of the PI3K/AKT pathway, one of the most important signaling pathways in human cancer. This pathway regulates the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol-3-phosphate (PIP3), which regulates multiple intracellular processes, including cell growth and proliferation. Pharmaceutical researchers have developed a variety of inhibitors against individual, or dual, components of this pathway [38, 39]. Recent clinical trial results, involving four cohorts of patients, reported no survival benefit from EGFR-targeted antigastric cancer therapy in advanced gastric cancer, with no genetic preselection of individuals. However, combining an EGFR tyrosine kinase inhibitor and a monoclonal antibody demonstrated greater efficacy and may represent a novel approach to treating gastric cancer [40]. The RAS mutation reportedly promotes gastric cancer cell proliferation and migration. Therefore, RAS inhibitors might offer a therapeutic option for gastric cancer [41]. Cancer cell survival, proliferation, and chemoresistance are affected by the MAPK signaling pathway, which mediates invasion and metastasis in gastric cancer [42]. These signaling pathways could exert synergistic mechanisms, through the index components of BXD, supporting a potential role in treating gastric cancer.

5. Conclusion

The current work employed an integrated approach to determine the pharmacological mechanism of BXD index components in gastric cancer. Six index components of BXD and 155 common targets against gastric cancer were involved. GO/KEGG enrichment analysis indicated that BXD index components exerted antigastric cancer activity through multiple biological processes and pathways, including PKB signaling, response to reactive oxygen species, proteoglycans in cancer, and the PI3K-Akt, Ras, and the MAPK signaling pathways. Molecular docking analysis showed good to strong affinities between the index components and the core targets for gastric cancer (ANXA5, CYP19A1, FGF1, and F2) obtained from Lasso regression analysis. Experimental validation of our results is warranted, but our findings pave the way for further investigation of the antigastric cancer activity and mechanisms of action of BXD.

Data Availability

The data used in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Acknowledgments

We thank Xiantao Academic for their contribution to data analysis and visualization. We would like to express our gratitude to EditSprings (https://www.editsprings.cn) for the expert linguistic services provided. This work was supported by the Health Commission of Qinghai Province (grant no. 2022-wjzdx-20) and the Qinghai Province Youth and Middle-Aged Science and Technology Talent Support Project (grant no. 2022QHSKXRCTJ08).

Supplementary Materials

The complete ADMET profiles for all compounds have been provided in Supplementary File S1. GO/KEGG enrichment results are presented in Supplementary Files S2–S5. Supplementary File S6 provides the molecular docking settings and results using Auto Dock Vina. (*Supplementary Materials*)

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