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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Basic Study

Curcumin for gastric cancer: Mechanism prediction via network pharmacology, docking, and *in vitro* experiments

Peng-Hui Yang, Ya-Nan Wei, Bi-Juan Xiao, Si-Yi Li, Xin-Long Li, Liang-Jun Yang, Hua-Feng Pan, Geng-Xin Chen

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Abstract

BACKGROUND

Curcumin originates from the natural herb turmeric, and its antitumor effects have been known about for a long time. However, the mechanism by which curcumin affects gastric cancer (GC) has not been elucidated.

AIM

To elucidate the potential mechanisms of curcumin in the treatment of GC.

METHODS

Network pharmacological approaches were used to perform network analysis of Curcumin. We first analyzed Lipinski's Rule of Five for the use of Curcumin. Curcumin latent targets were predicted using the PharmMapper, SwissTargetPrediction and DrugBank network databases. GC disease targets were mined through the GeneCard, OMIM, DrugBank and TTD network databases. Then, GO enrichment, KEGG enrichment, protein-protein interaction (PPI), and overall survival analyses were performed. The results were further verified through molecular docking, differential expression analysis and cell experiments.

RESULTS

We identified a total of 48 curcumin-related genes with 31 overlapping GC-related targets. The intersection targets between curcumin and GC have been enriched in 81 GO biological processes and 22 significant pathways. Following PPI analysis, 6 hub targets were identified, namely, *estrogen receptor 1 (ESR1)*, *epidermal growth factor receptor (EGFR)*, *cytochrome P450 family 3 subfamily A member 4 (CYP3A4)*, *mitogen-activated protein kinase 14 (MAPK14)*, *cytochrome P450 family 1 subfamily A member 2 (CYP1A2)*, and *cytochrome p450 family 2 subfamily B member 6 (CYP2B6)*. These factors are correlated with decreased survival rates among patients diagnosed with GC. Molecular docking analysis further substantiated the strong binding interactions between Curcumin and the hub target genes. The experimental findings demonstrated that curcumin not only effectively inhibits the growth of BGC-823 cells but also suppresses their proliferation. mRNA levels of hub targets *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6* in BGC-823 cells were significantly increased in each dose group.

CONCLUSION

Curcumin can play an anti-GC role through a variety of targets, pathways and biological processes.

Key Words: Curcumin; Gastric cancer; Network pharmacology; Molecular docking; Survival analysis

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Core Tip: This study aimed to elucidate the therapeutic mechanisms of curcumin in gastric cancer (GC). Through network pharmacology, core targets correlating to poor survival in patients with GC were identified, including *estrogen receptor 1 (ESR1)*, *epidermal growth factor receptor (EGFR)*, *cytochrome P450 family 3 subfamily A member 4 (CYP3A4)*, *mitogen-activated protein kinase 14 (MAPK14)*, *cytochrome P450 family 1 subfamily A member 2 (CYP1A2)*, and *cytochrome p450 family 2 subfamily B member 6 (CYP2B6)*. Molecular docking confirmed the favorable interactions of curcumin with pivotal target genes. *In vitro* experiments validated the regulatory effects of curcumin on GC cells through these targets. The therapeutic efficacy of curcumin involves multitarget, multipathway, and multibiological processes, offering new insights into its clinical application in GC treatment.

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INTRODUCTION

Gastric cancer (GC) poses a significant threat to human health, with the highest incidence rates observed in East Asia, particularly in China where it ranks third among all cancer incidences, thus constituting a significant public health concern[1,2]. Despite ongoing advancements in treatment modalities for GC, the treatment prospects for patients with advanced GC remain unsatisfactory due to primary or acquired drug resistance and the limited availability of effective treatment methods. However, 5-year survival rate for individuals diagnosed with GC is below 20%[3]. Therefore, the demand for new agents, especially drugs extracted from natural resources, continues to increase.

Natural products are treasures from the natural world, serving not only as treatments for various ailments but also as crucial reservoirs for synthesizing therapeutic drugs[4]. Curcumin, a bioactive phytochemical compound belonging to the Zingiberaceae family, is naturally abundant in the rhizomes of turmeric plants and is notably rich in phenol (diferuloylmethane)[5]. Prior research has indicated that the primary physiological activity of curcumin lies in its anti-inflammatory and antioxidative effects; thus, curcumin exerts an efficient antitumoral effect and plays a significant role in anti-inflammatory and antitumor treatment[6,7]. In addition, accumulating evidence has shown that curcumin can not only induce tumor apoptosis by regulating cyclin kinases and their inhibitors through the p53-dependent signaling pathway but also regulate several transcription factors, including the STAT protein, NF-κB protein, and multiple signaling pathways, to inhibit tumor vascular formation[8,9]. However, the mechanism by which curcumin affects GC has not been fully revealed.

Network pharmacology has become a powerful means to understand the potential action of traditional Chinese medicine in cancer treatment. To better explore the therapeutic potential of curcumin in treating GC, we employed a network pharmacology approach to investigate its mechanisms of action.

MATERIALS AND METHODS

Drug similarity

Lipinski's Rule of Five (RO5) is a set of guidelines used to assess the potential suitability of oral drugs by assessing drug likeness. Including the molecular weight (MW), hydrophobicity (XLogP3), polar surface area, rotatable bonds, H-bond acceptors, and H-bond donors. To explore curcumin's similarity, the SMILES database (COC1=C(C=CC(=C1)C=CC(=O)CC(=O)C=CC2=CC(=C(C=C2)O)OC)O) was uploaded to the SwissADME network tool to evaluate the physicochemical properties, pharmacokinetics, drug similarity, and chemical friendliness of the drug, which was subsequently screened by referring to the default parameters[10,11].

Prediction of the molecular targets of curcumin

Identifying drug component targets is indispensable in drug discovery, facilitated by unique technologies that pinpoint the genes and proteins associated with the drug. To ensure the comprehensive collection of curcumin, the PharmMapper, Swiss TargetPrediction and DrugBank databases were used for prediction[12,13]. According to the Swiss TargetPrediction database, a correlation value ≥ 0.7 was selected as the molecular target of curcumin. To standardize the gene symbols and facilitate subsequent data sorting, the predicted curcumin targets were sent to UniProt database unified gene symbol after the molecular targets were obtained.

Prediction of GC target genes

To comprehensively enrich the disease-related targets, we collected GC targets from various public databases, namely, the GeneCard database, the Online Mendelian Inheritance in Man (OMIM) database, the DrugBank database and the TTD database. Notably, targets with a score greater than 10 in the GeneCards database were selected as genes related to GC. We then integrated the disease targets of the four databases and represented each target with the gene symbol uniformly. Eventually, the targets related to the pathogenesis of GC were identified[14].

Cross-sectional relationships between molecular targets and disease targets

The target genes of curcumin and GC were introduced into the Weishengxin online mapping tool to identify the putative intersection genes of the drug molecule and the disease target.

Protein interaction network for turmeric and GC intersection-PPIs

The obtained curcumin-related genes and GC-related genes were integrated and then analyzed using the STRING database. Settings were adjusted to "*Homo sapiens*" and an interaction score of " ≥ 0.4 ". After obtaining the protein interaction TSV format file, the data were imported to Cytoscape (version Cytoscape_v3.7.2) software for analysis *via* network visual processing, and subsequently, the curcumin-GC target visual network was successfully constructed.

Selection of hub targets

We obtained the connection score between targets through the cythubba tool downloaded from Cytoscape (version Cytoscape_v3.7.2), and then, the hub targets were obtained by Maximal Clique Centrality (MCC) score screening. The network was visualized to obtain the length of the hub target network.

KEGG and GO analysis

After integrating the hub targets, KEGG and GO analyses were performed on these targets using the DAVID database, proceeded with data mining and visual analysis of the impact of curcumin on GC.

Overall survival analysis of patients stratified by hub gene expression

Prognosis holds significant evaluative value in cancer treatment. The prognostic significance of hub targets in GC patients was assessed using the Kaplan-Meier plotter[15]. In the GC dataset, GC patients were divided into high and low expression groups. Hazard ratios, logarithmic rank *P* values, and their corresponding 95%CI were computed. Comparative analysis was performed using Kaplan-Meier survival curves.

Molecular docking verification

To further ascertain the relationship and mechanism of the interaction of candidate proteins with curcumin, through molecular docking, we can effectively evaluate the binding affinity between curcumin and hub targets. Firstly, the three-dimensional structure of the small molecule was obtained and subjected to energy minimization, followed by saving it in mol2 format. Subsequently, the optimized small molecule was loaded into AutodockTools-1.5.6 for hydrogenation, charge calculation, and charge distribution. After configuring the rotatable bonds, the file was saved in "pdbqt" format. Next, the protein structure corresponding to the provided PDB ID was retrieved from the PDB database. Using PyMOL 2.3.0 software, water molecules and native ligands were removed from the protein crystal structure, which was then loaded into AutoDockTools (v1.5.6) for hydrogenation. Following this, the charge, distribution, and specific atom types of the protein were computed, and the data were saved in "pdbqt" format. Finally, molecular docking simulations were conducted using AutoDock Vina 1.1.2.

Differential expression analysis

The expression levels of *estrogen receptor 1 (ESR1)*, *epidermal growth factor receptor (EGFR)*, *cytochrome P450 family 3*

Table 1 Primer sequences

Genes	Primers (5' to 3')
ESR1	F: AGTGCCTTGTGGATGCT
	R: TGCCAGGTTGGTCAGTAAG
EGFR	F: GGGTGCAGGAGAGGAGAA
	R: CTGGTTGTGGCAGCAGTC
CYP3A4	F: ATGGCACCGTAAGTGGAG
	R: TGGTGTTCACAGGCACAG
MAPK14	F: AATACTGGGGAGGGGACA
	R: GGCTTCATTCGTTTTTCGTT
CYP1A2	F: AGAATGCCCTCAACACCTT
	R: CCTTGCTCACATGCTCCT
CYP2B6	F: GTCTCCCCAGTCCCTCATT
	R: AGTGCAGAATCCCACAGC
GAPDH	F: TGIGTCCGTCGGATCTGA
	R: TTGCTGTTGAAGTCGCAGGAG

ESR1: Estrogen receptor 1; EGFR: Epidermal growth factor receptor; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; MAPK14: Mitogen-activated protein kinase 14; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2B6: Cytochrome P450 family 2 subfamily B member 6.

subfamily A member 4 (CYP3A4), mitogen-activated protein kinase 14 (MAPK14), cytochrome P450 family 1 subfamily A member 2 (CYP1A2), and cytochrome p450 family 2 subfamily B member 6 (CYP2B6) genes in GC and normal tissues were analyzed using UALCAN (<http://ualcan.path.uab.edu/>). Utilizing the TCGA database, UALCAN was employed to study the expression levels of these hub targets in clinical tissue samples.

Analysis of the ability of curcumin to inhibit the proliferation of BGC-823 GC cells

Curcumin was dissolved in 0.1% DMSO (manufactured by Sigma) and subsequently diluted in culture medium to prepare solutions with final concentrations of 0, 10, 20, 40, and 80 $\mu\text{mol/L}$. Log-phase BGC cells were seeded at a density of 2×10^6 cells per well in 6-well plates. GC BGC cells were subjected to treatment with varying concentrations of each concentration of curcumin as described above in five parallel wells and cultured for 24 hours and 48 hours. Following that, a certain amount of CCK8 was added to each well in a 96-well plate, and the plate was placed in a 37 °C incubator in the dark for 1.5 hours. Absorbance values were measured at a wavelength of 472 nm using a microplate reader, and data were statistically analyzed to calculate the cell survival rate.

Expression of hub targets in curcumin-treated BGC-823 cells measured by qRT-PCR

The logarithmic growth phase BGC-823 cells were grouped and treated with curcumin solutions at final concentrations of 0, 10, 20, 40, and 80 $\mu\text{mol/L}$. After 24 hours of incubation, cells from each group were harvested, and RNA was extracted and quantified. Subsequently, reverse transcription and RT-qPCR were performed. The primer sequences are listed in Table 1. A summary of all databases utilized in this study is provided in Table 2.

RESULTS

Molecular properties of curcumin

Our results showed that the MW was less than five hundred; the numbers of hydrogen bond donors and receptors were less than 5 and 10, respectively; the number of rotating bonds was not more than ten; and the lipid-water distribution coefficient was less than 5. The results revealed that the nature of curcumin conforms to Lipinski's RO5, which strongly indicates that it has good drug class properties (Table 3).

Building a molecular drug target and disease target database

Drugs can usually be combined with multiple targets, namely, multiple pharmacological agents or drugs. Thus, the present study predicted the latent targets of curcumin. After the target data were merged, forty-eight replicates of curcumin were saved. The genes associated with GC were then retrieved from the GeneCard, OMIM, Drugbank, and TTD databases. Subsequently, 1508 GC targets were obtained after eliminating redundant data from the above database, by integrating the targets of curcumin and GC, we identified 31 common targets as potential targets for curcumin in the

Table 2 Databases and online tools

Database/tool	Use/version	Database website/version
SwissADME	Drug similarity prediction	http://www.swissadme.ch
PharmMapper database	Molecular target prediction	http://www.lilab-ecust.cn/pharmmapper/
Swiss TargetPrediction database		http://www.swisstargetprediction.ch/
Drugbank database		www.drugbank.ca
GeneCard database	Disease target prediction	https://www.genecards.org/
OMIM database		https://omim.org/
TTD database		http://db.idrblab.net/ttd/
Drugbank database		www.drugbank.ca
String database	Protein InterNetNetwork	https://string-db.org/
Cytoscape tool		Cytoscape_v3.7.2
cythubba tool	Hub target filtering	Cytoscape_v3.7.2
DAVID database	KEGG and GO Analysis	https://david.ncifcrf.gov/
Kaplan-Meier tool	Survival analysis	https://kmplot.com/analysis/
AutoDock Vina	Molecular docking	AutoDock Vina1.1.2
Bioinformatics tool	Visualization drawing	http://www.bioinformatics.com.cn/
Ualcan	TCGA	http://ualcan.path.uab.edu/

Table 3 Molecular properties of curcumin

Property	Value
Molecular weight	368.38 g/mol
PSA	93.06 Å ²
XLogP3	3.20
Rotatable bonds	8
H-bond donor	2
H-bond acceptor	6
Molar refractivity	102.80
Bioavailability score	0.55

PSA: Polar surface area.

treatment of GC (Figure 1).

A composite target network was established

To explore the connections between the potential targets and curcumin, we constructed a composite target network. The network, comprising curcumin and the potential targets, included 32 nodes and 31 edges, as depicted in Figure 2.

Visualization and integration of protein interaction networks

To better understand proteins within cells at a systemic level, through STRING database, we constructed a PPI network consisting of thirty-one targets related to curcumin (Figure 3). Based on the topological analysis of the PPI network, the color varied from yellow to red as the score increased, with ESR1 being the deepest and greatest (MCC score = 732). On the basis of the calculations of the cythubba data, six targets, namely, ESR1, EGFR, CYP3A4, MAPK14, CYP1A2, and CYP2B6, were selected as hub targets based on PPI topological analysis, indicating that they may have significant potential impact on the development of GC, as illustrated in Figure 3.

GO analysis

To better analyze the potential biological processes and cellular molecular mechanisms of curcumin in the treatment of

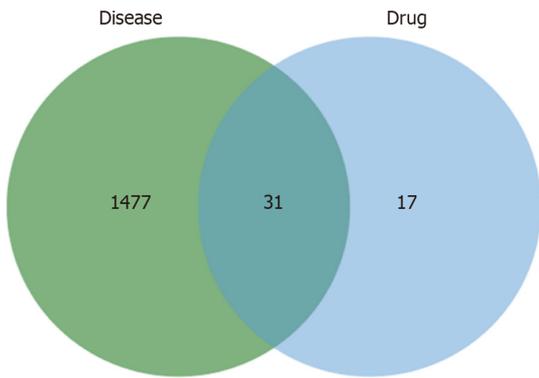


Figure 1 Curcumin–GC overlapping genes. The green circle on the left represents the disease targets corresponding to gastric cancer, while the blue circle on the right represents the compound targets corresponding to curcumin. The dark blue area indicates the intersection targets between curcumin and gastric cancer.

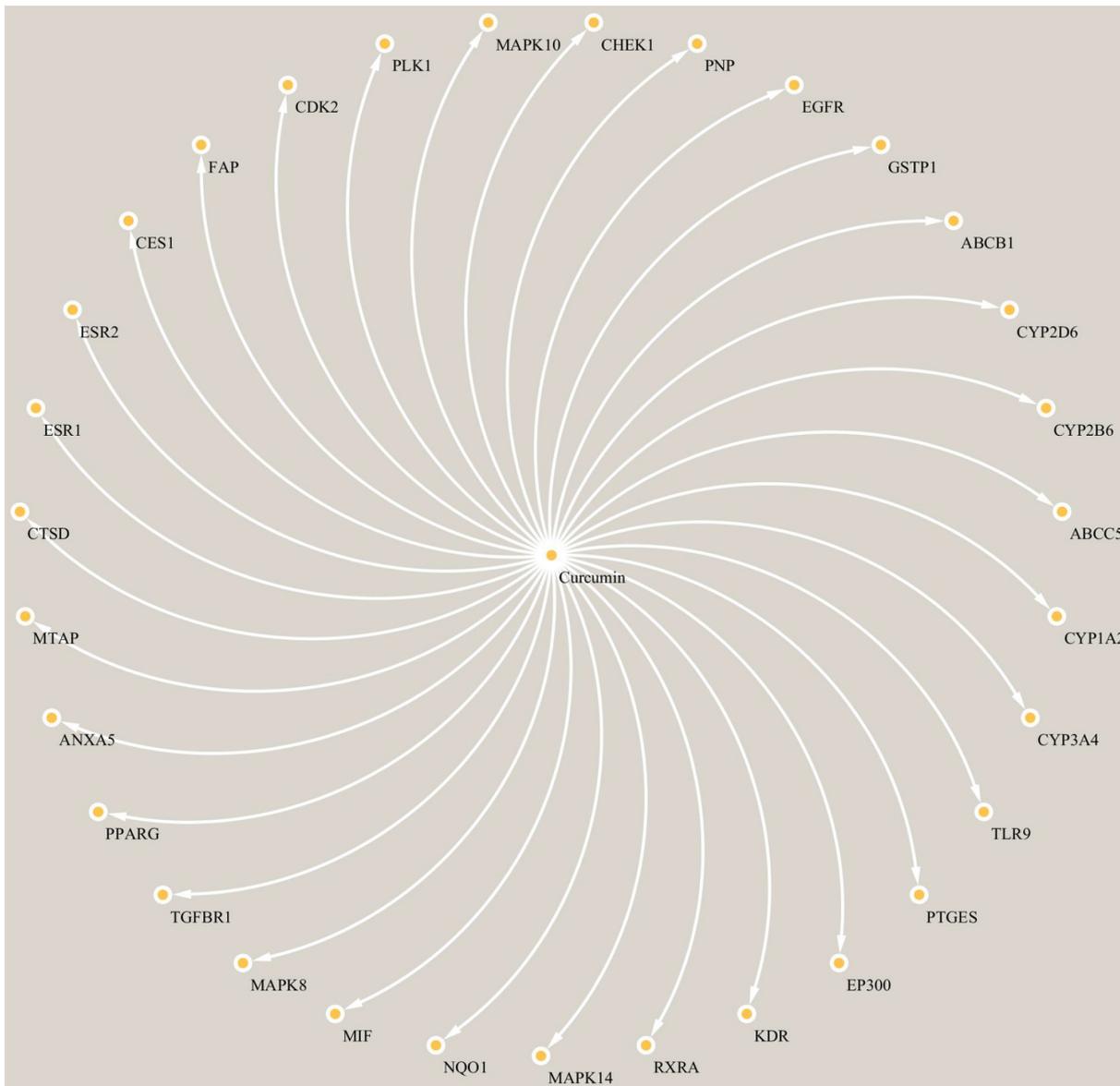


Figure 2 Compound–target network. The mutual network between curcumin (central orange node) and its intersection targets (peripheral orange nodes) included 32 nodes and 31 edges. ESR1: Estrogen receptor 1; EGFR: Epidermal growth factor receptor; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; MAPK14: Mitogen-activated protein kinase 14; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2B6: Cytochrome P450 family 2 subfamily B member 6.

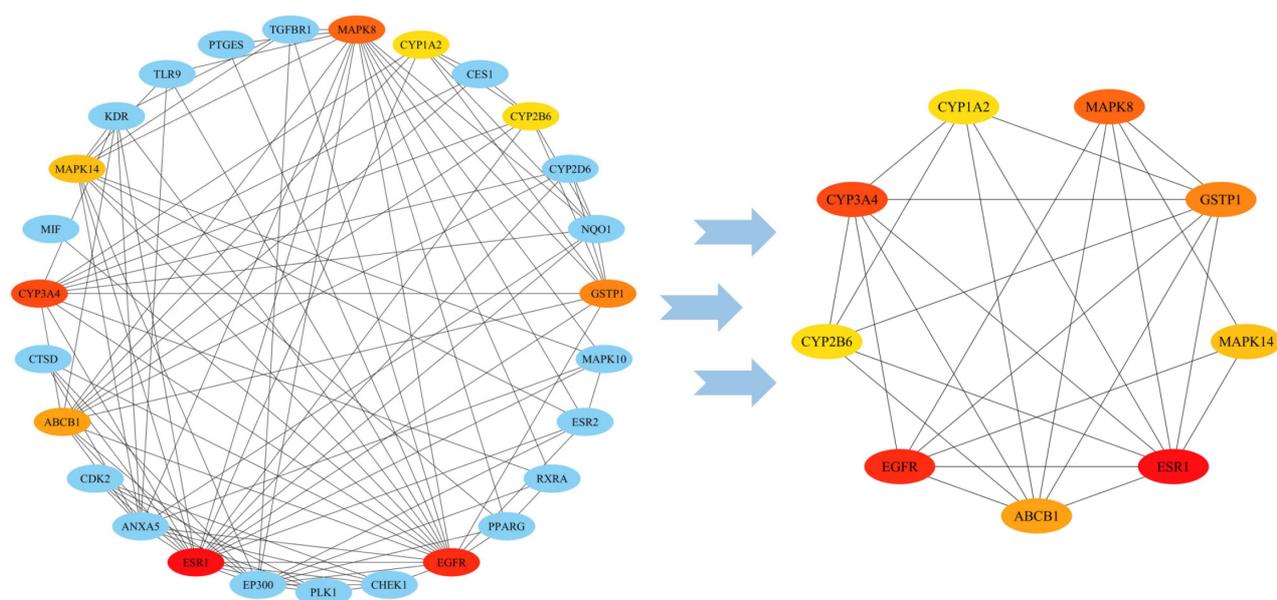


Figure 3 Protein-protein interaction network. The network on the left represents the topological analysis of the network for curcumin–gastric cancer intersection targets, with the color becoming increasingly red as the degree value increases. The network on the right represents the topological graph of the target gene network with the top 8 degree values. *ESR1*: Estrogen receptor 1; *EGFR*: Epidermal growth factor receptor; *CYP3A4*: Cytochrome P450 family 3 subfamily A member 4; *MAPK14*: Mitogen-activated protein kinase 14; *CYP1A2*: Cytochrome P450 family 1 subfamily A member 2; *CYP2B6*: Cytochrome P450 family 2 subfamily B member 6.

GC, we performed GO analysis on 31 potential targets of curcumin for GC treatment. Based on the analysis results, we found that the potential targets were enriched in 81 GO biological processes, including 18 cell component terms, 42 molecular function terms, and the first 20 biological processes, first 5 cellular components, and first 10 molecular functions are presented in Figure 4. As shown in Figure 4, the first 20 biological process terms were significantly associated with "GO:0007165" (GO:0007165), "Negative regulation of apoptotic processes" (GO:0043066), and "Foreign Body Metabolic Process" (GO:0006805). The first 5 cell component terms were significantly associated with the visible sites of action according to GO:0005737 and GO:0005634. The first 10 molecular function terms were significantly associated with "protein binding" (GO:0005515), "ATP binding" (GO:0005524), and "enzyme binding" (GO:0019899). The findings showed that potential targets regulate cell signal transduction, proliferation, apoptosis, phosphorylation, oxidative stress, and metabolism.

KEGG analysis

For a deeper comprehending of pharmacological mechanisms underlying efficacy of curcumin in GC, we performed a KEGG pathway analysis of these thirty-one targets *via* the DAVID database. The results showed that 31 targets were associated with 46 pathways. Combined with the pathogenesis and gene count of GC (gene count ≥ 3), GC-independent pathways such as the prolactin signaling pathway (KEGG: Hsa04917), tuberculosis (KEGG: Hsa05152), and pancreatic cancer (KEGG: Hsa05212) were eliminated. Finally, ten significant enrichment approaches may be the main approaches for GC treatment (as shown in Table 4). A pathway enrichment diagram was then generated by mapping the targets through bioinformatics tools (Figure 5). The aforementioned results indicate that curcumin plays a therapeutic role through FOXO and other signaling pathways that affect cancer.

Survival analysis

Using the Kaplan-Meier plot database for survival analysis of the hub targets, we have observed high expression of targets (including *ESR1*, *EGFR*, *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6*) was linked to poor survival in GC patients, as shown in Figure 6.

Molecular docking

Through molecular docking verification analysis, curcumin was found to be stable in docking with the hub targets *ESR1*, *EGFR*, *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6*, and the binding energy was low (Table 5). Further examination of results revealed that curcumin exhibited strong binding affinity to *CYP1A2*, forming hydrogen bonds at Arg108 (A) and Arg456 (A) with lengths of 3.15 Å and 3.15 Å, respectively, and the binding energy was -9.5 kcal/mol. Curcumin has a good binding effect on *CYP2B6*, forming hydrogen bonds at Arg98 (A) with lengths of 2.95 Å and 2.96 Å, and the binding energy was -9.3 kcal/mol. There was good interaction between curcumin and *CYP3A4* only through hydrophobic interactions, and the binding energy was -8.4 kcal/mol. Curcumin has good binding affinity for *MAPK14*, forming a hydrogen bond at Lys53 (A) with a length of 3.22 Å, and the binding energy was -7.9 kcal/mol. Curcumin has good binding with *EGFR*, forming a hydrogen bond at Lys745 (A) with a length of 3.31 Å, and the binding energy was -7.8

Table 4 Top 10 representative pathways according to gene count

Pathway ID	Pathway	Corrected P value	Gene count	Annotated genes
KEGG: hsa04068	FoxO signaling pathway	7.66E-07	8	MAPK10, MAPK8, PLK1, CDK2, EP300, MAPK14, EGFR, TGFBR1
KEGG: hsa05200	Pathways in cancer	1.19E-04	9	MAPK10, MAPK8, RXRA, GSTP1, CDK2, EP300, PPARG, EGFR, TGFBR1
KEGG: hsa00982	Drug metabolism - cytochrome P450	1.50E-04	5	CYP2B6, CYP2D6, GSTP1, CYP1A2, CYP3A4
KEGG: hsa00980	Metabolism of xenobiotics by cytochrome P450	2.08E-04	5	CYP2B6, CYP2D6, GSTP1, CYP1A2, CYP3A4
KEGG: hsa05120	Epithelial cell signaling in <i>Helicobacter pylori</i> infection	0.002430862	4	MAPK10, MAPK8, MAPK14, EGFR
KEGG: hsa04912	GnRH signaling pathway	0.00577562	4	MAPK10, MAPK8, MAPK14, EGFR
KEGG: hsa04620	Toll-like receptor signaling pathway	0.008806272	4	MAPK10, MAPK8, TLR9, MAPK14
KEGG: hsa04071	Sphingolipid signaling pathway	0.012342719	4	MAPK10, MAPK8, MAPK14, CTSD
KEGG: hsa05169	Epstein-Barr virus infection	0.012905562	4	MAPK10, MAPK8, CDK2, MAPK14
KEGG: hsa04110	Cell cycle	0.013483025	4	PLK1, CHEK1, CDK2, EP300

ESR1: Estrogen receptor 1; EGFR: Epidermal growth factor receptor; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; MAPK14: Mitogen-activated protein kinase 14; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2B6: Cytochrome P450 family 2 subfamily B member 6.

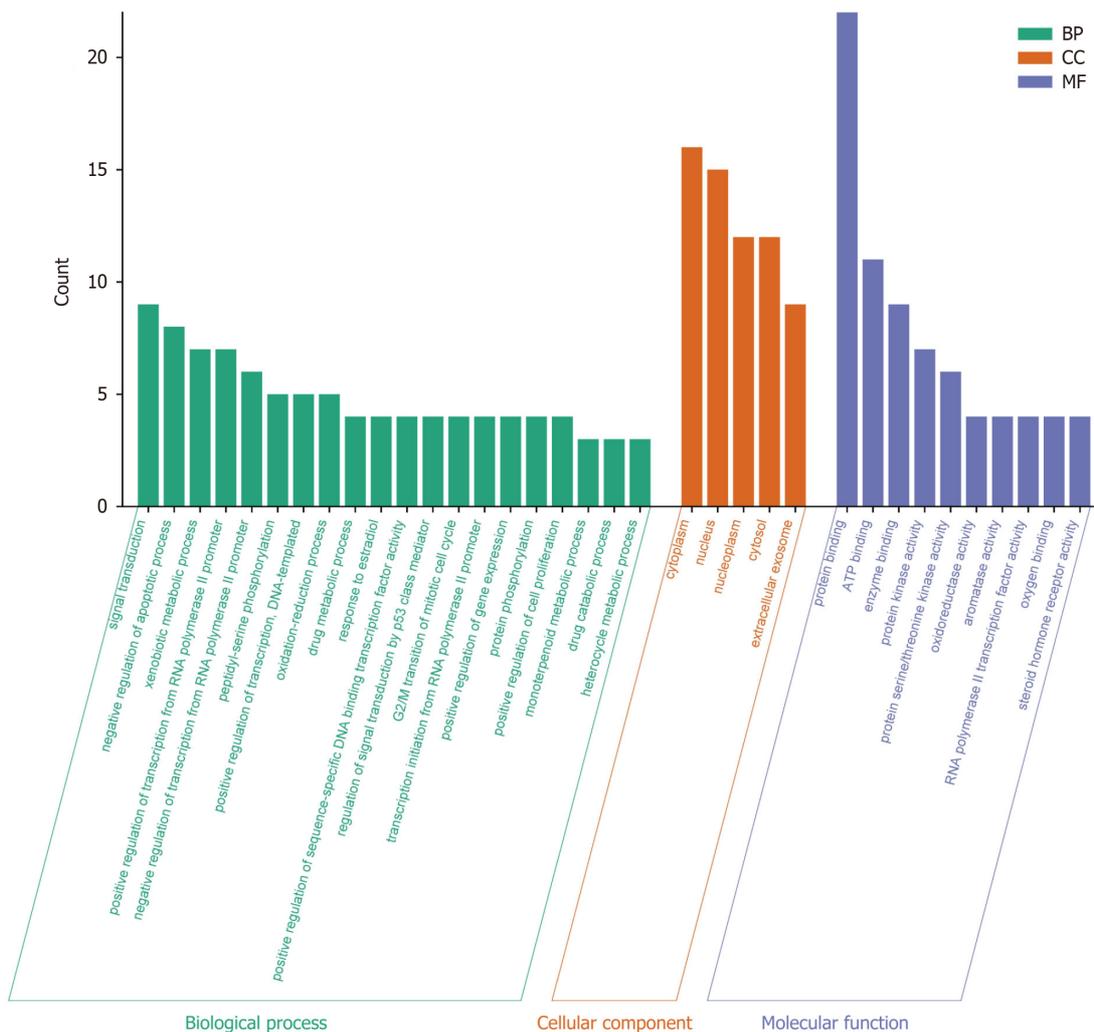


Figure 4 GO analysis of target genes. BP: Biological process; CC: Cellular component; MF: Molecular function.

Table 5 Binding information for curcumin and docking of the hub target molecules

Hub targets	Binding energy (kcal/mol)	Hydrogen bonds			Hydrogen bonds, lengths			
ESR1	-6.3	Ala307 (A)	Gly366 (A)	Ser305 (A)	2.82Å	3.06Å	2.95Å	3.47Å
EGFR	-7.8	Lys745 (A)			3.31Å			
CYP3A4	-8.4	-			-			
MAPK14	-7.9	Lys53 (A)			3.22Å			
CYP1A2	-9.5	Arg108 (A)		Arg456 (A)	3.15Å		3.15Å	
CYP2B6	-9.3	Arg98 (A)			2.95Å		2.96Å	

ESR1: Estrogen receptor 1; EGFR: Epidermal growth factor receptor; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; MAPK14: Mitogen-activated protein kinase 14; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2B6: Cytochrome P450 family 2 subfamily B member 6.

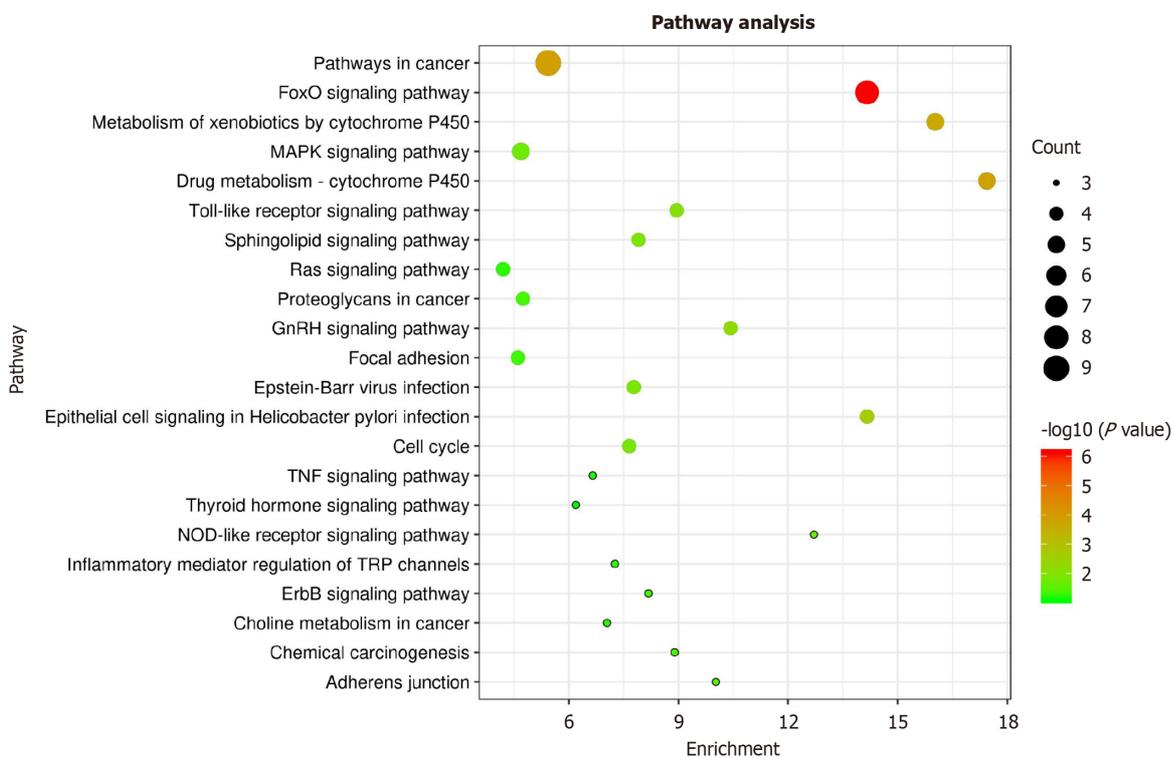


Figure 5 KEGG analysis of target genes.

kcal/mol. Curcumin exhibited strong binding affinity to ESR1, forming hydrogen bonds with Ala307 (A), Gly366 (A) and Ser305 (A), with lengths of 2.82 Å, 3.06 Å, 2.95 Å and 3.47 Å, respectively. The binding energy was -6.3 kcal/mol (Figure 7).

Differential hub genes expression analysis

According to the TCGA database, grouping 415 GC tissue samples and 34 normal tissue samples, and analyzing their differential gene expression levels. We found that the levels of expression of EGFR, CYP3A4, MAPK14 and CYP2B6 varied significantly between GC and normal tissues (P < 0.05), while the expression levels of ESR1 and CYP1A2 were not significantly different (Figure 8).

Curcumin inhibits the proliferation of BGC-823 cells

Figure 9 shows that following treatment with curcumin for 24 hours and 48 hours, compared with that after treatment with 0 µmol/L curcumin, cell growth was significantly inhibited after treatment with 10, 20, 40, 80 µmol/L curcumin. At the same time, the higher the concentration of curcumin was, the more obvious was the inhibition of cell growth. Statistical significance was observed when the concentration of curcumin was greater than or equal to 20 µmol/L (P < 0.001).

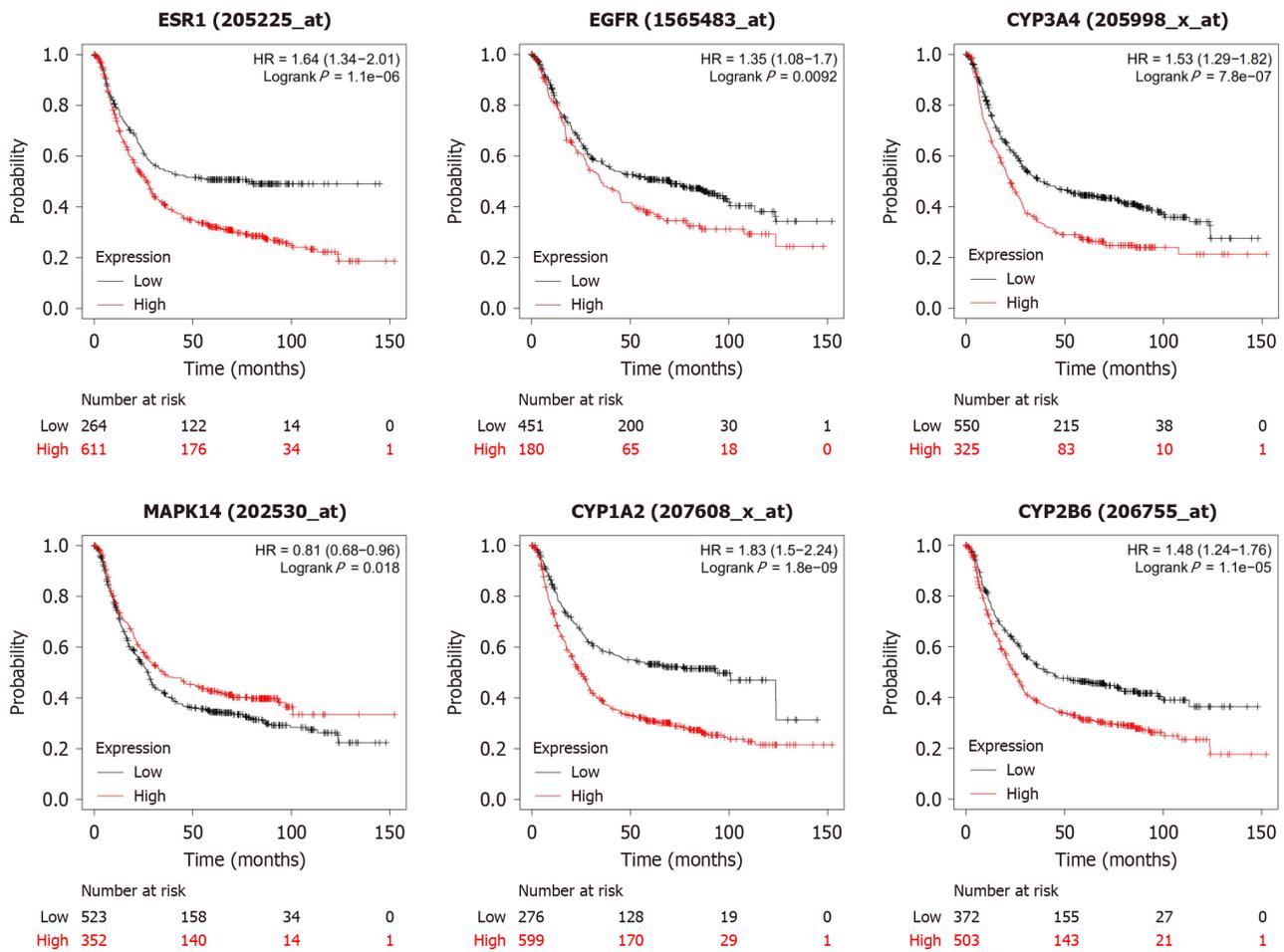


Figure 6 Prognostic value evaluation of the expression of the six hub targets. Survival data were analyzed by the Kaplan-Meier plotter database ($P < 0.05$); red lines represent patients above the median, and black lines represent patients below the median. HR: Hazard ratio; *ESR1*: Estrogen receptor 1; *EGFR*: Epidermal growth factor receptor; *CYP3A4*: Cytochrome P450 family 3 subfamily A member 4; *MAPK14*: Mitogen-activated protein kinase 14; *CYP1A2*: Cytochrome P450 family 1 subfamily A member 2; *CYP2B6*: Cytochrome P450 family 2 subfamily B member 6.

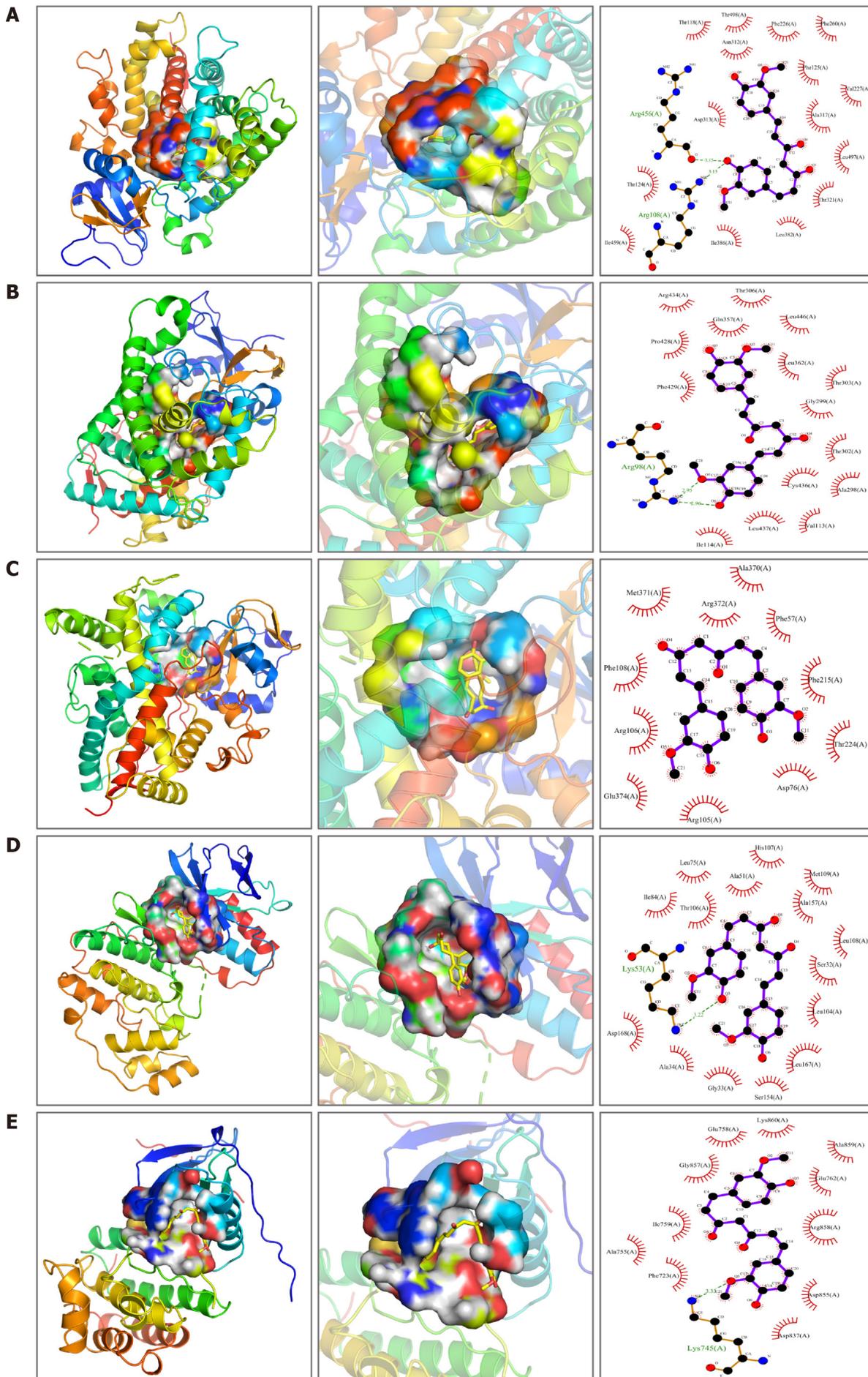
Effect of curcumin on hub targets expression in BGC-823 cells

The experimental results revealed a significant increase in the mRNA expression levels of *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6* in BGC-823 cells treated with curcumin compared to the 0 $\mu\text{mol/L}$ curcumin group ($P < 0.05$, 0.01, 0.001; Figure 10). Statistical analysis revealed a significant reduction in the mRNA levels of *EGFR* when the concentration of curcumin reached or exceeded 40 $\mu\text{mol/L}$ ($P < 0.01$, 0.001). After intervention with a certain concentration of curcumin, significant differences were observed in the mRNA levels of hub target genes across all groups, except for *ESR1*.

DISCUSSION

Curcumin as diketone compound derived from rhizome of some plants in the Zingiberaceae and Araceae. It possesses a diverse array of biological functions, including anti-inflammatory, antitumor and antioxidant effects[16]. Its anticancer effects primarily stem from its ability to negatively regulate multiple transcription factors and inhibit cellular proliferation, through eliminating stasis cancer cells at various phases of cell cycle or inducing their apoptosis[17]. Curcumin has been proven to be capable of treating GC by inhibiting cell proliferation, inducing apoptosis, and reducing chemotherapy resistance. Thus, the use of curcumin is a novel and promising treatment strategy for controlling progression of GC cells[18]. However, the specific molecular pathways through which curcumin treats GC have not been completely elucidated. Our current study used a network pharmacology approach and conducted a series of experiments, including drug similarity evaluation, target identification, GO and KEGG analysis, PPI analysis, gene survival analysis, molecular docking and experimental validation, to systematically analyze the molecular basis of curcumin's effects on GC treatment. Based on the RO5 parameters, curcumin demonstrates favorable pharmaceutically favorable characteristics, indicating it has broad prospects for pharmaceutical applications.

Fifteen GC targets were selected, referring to 81 biological processes, 18 cell components and 42 molecular functions. These biological processes mainly involve signal transduction, apoptosis, cell metabolism, proliferation, oxidative stress, and the cell cycle; cell components mainly involve the cytoplasm, nucleus, mitochondria, and cell membrane; molecular functions mainly involve protein binding, protein kinase activity, ATP binding, and enzyme binding. An essential charac-



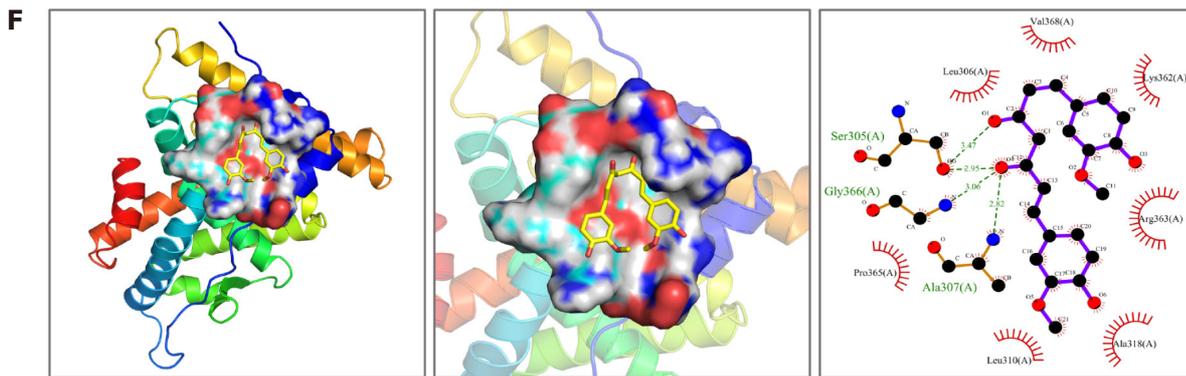


Figure 7 Docking results of curcumin and the six hub targets. A: *Cytochrome P450 family 1 subfamily A member 2*; B: *Cytochrome P450 family 2 subfamily B member 6*; C: *Cytochrome P450 family 3 subfamily A member 4*; D: *Mitogen-activated protein kinase 14*; E: *Epidermal growth factor receptor*; F: *Estrogen receptor 1*.

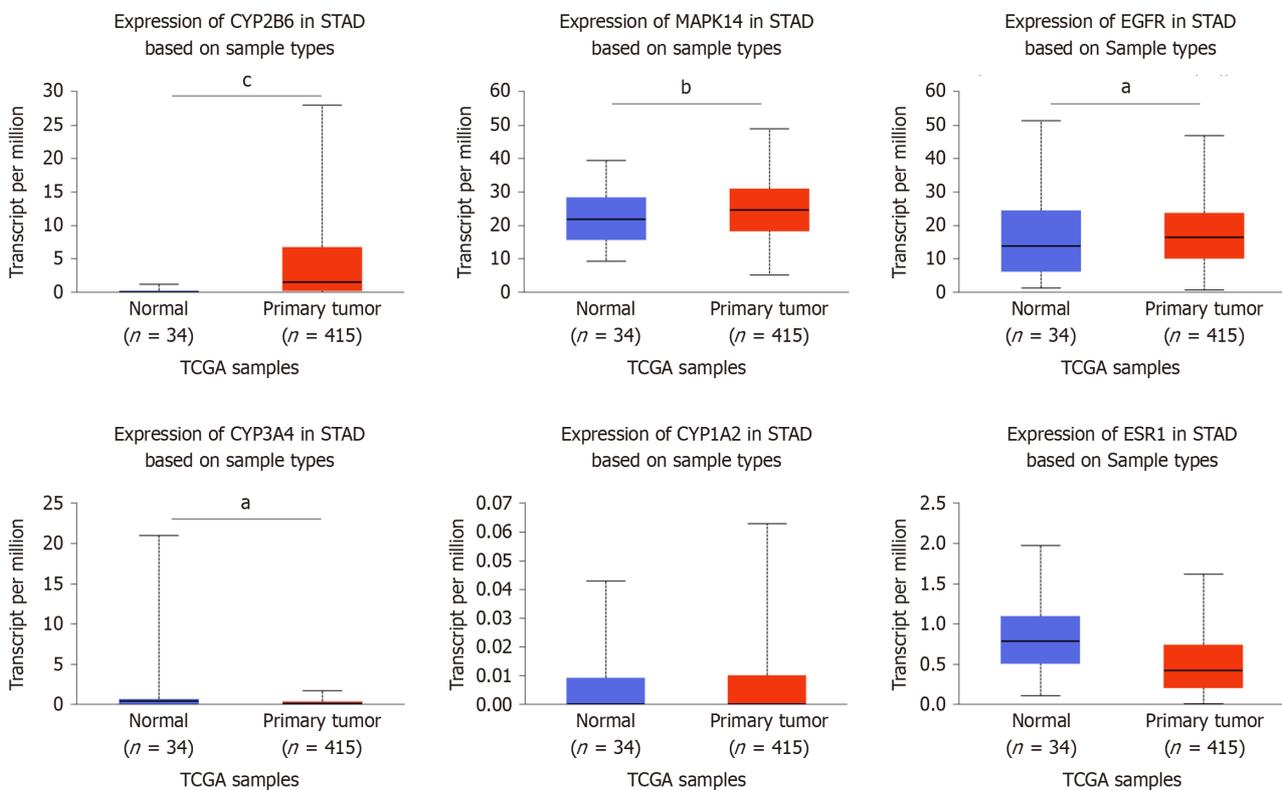


Figure 8 Expression of the *estrogen receptor 1*, *epidermal growth factor receptor*, *cytochrome P450 family 3 subfamily A member 4*, *mitogen-activated protein kinase 14*, *cytochrome P450 family 1 subfamily A member 2*, and *cytochrome p450 family 2 subfamily B member 6* genes in gastric cancer tissue and normal gastric tissue. ^a*P* < 0.05 vs normal group; ^b*P* < 0.01; vs normal group; ^c*P* < 0.001 vs normal group. ESR1: *Estrogen receptor 1*; EGFR: *Epidermal growth factor receptor*; CYP3A4: *Cytochrome P450 family 3 subfamily A member 4*; MAPK14: *Mitogen-activated protein kinase 14*; CYP1A2: *Cytochrome P450 family 1 subfamily A member 2*; CYP2B6: *Cytochrome P450 family 2 subfamily B member 6*.

teristic of cancer cells involves aberrant alterations in both proliferation and apoptosis. Therefore, a promising strategy for treating GC is to regulate the balance between GC cell proliferation and apoptosis. Multiple research findings suggest that manipulating apoptosis holds potential as an effective strategy for cancer treatment. Interruption of orderly apoptosis leads to the overgrowth of malignant cells[19]. Studies have shown that curcumin can significantly activate the activity of Caspase-3 and cleaved PARP to induce apoptosis in GC cells[20]. Furthermore, curcumin can significantly reduce the proliferative capacity of tumors by blocking the cell cycle progression[21]. The rising prominence of metabolomics has led to heightened interest among researchers in understanding the association between metabolic regulation and cancer. Impairment of mitochondrial metabolic reactions leads to the production of reactive species, such as ROS, which are known to instigate oxidative stress and provoke cellular damage, thereby disrupting normal physiological functions. Prolonged elevation of ROS levels can induce the activation of oncogenes, genetic mutations, or chromosomal abnormalities[22,23].

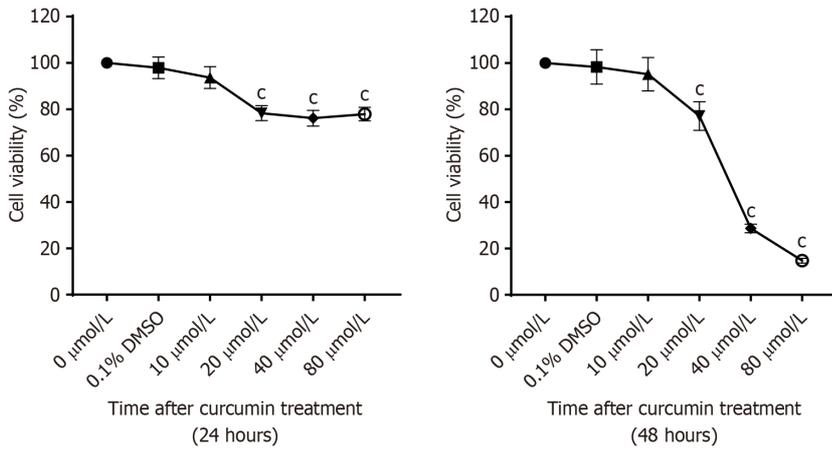


Figure 9 Inhibitory effect of different concentrations of curcumin on the proliferation of BGC-823 cells. ^a*P* < 0.001 vs 0 μmol/L.

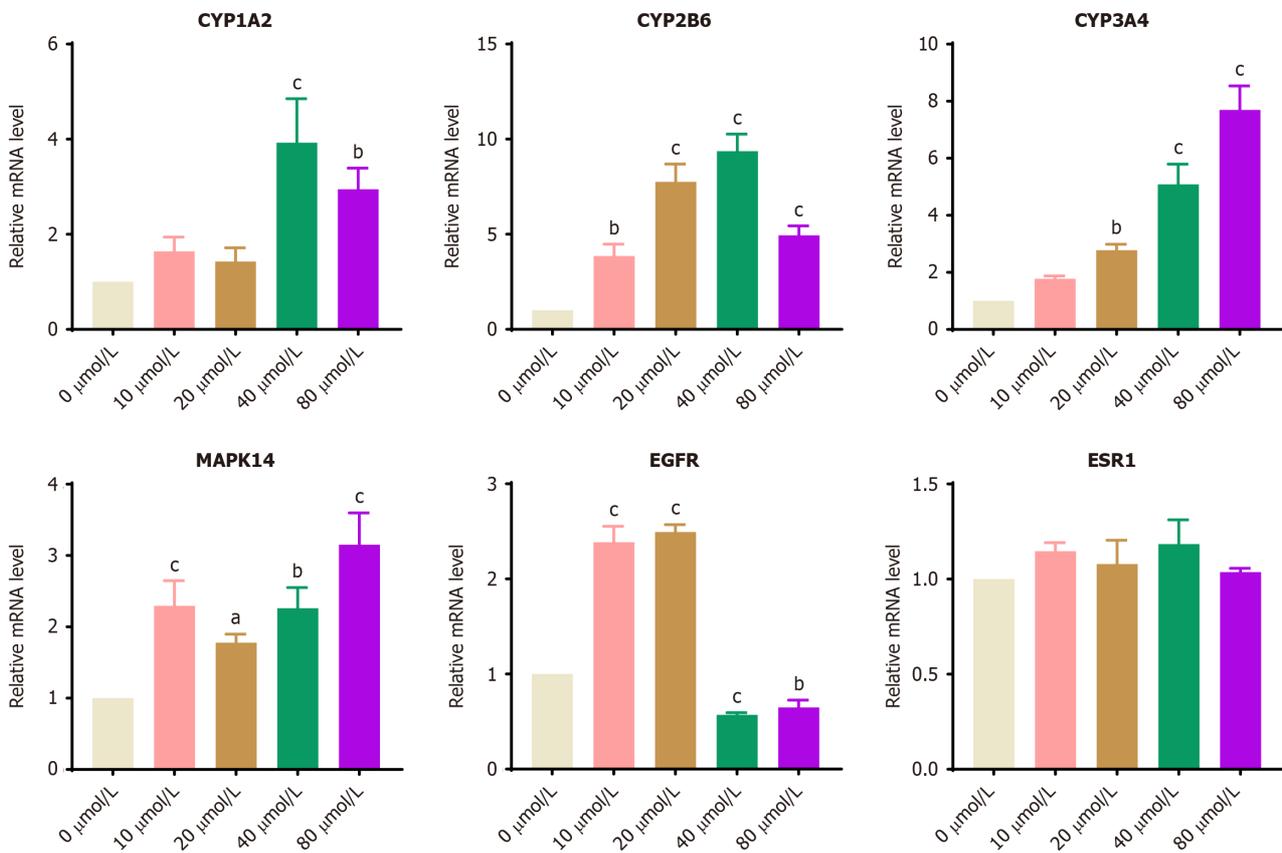


Figure 10 The mRNA expression levels of estrogen receptor 1, epidermal growth factor receptor, cytochrome P450 family 3 subfamily A member 4, mitogen-activated protein kinase 14, cytochrome P450 family 1 subfamily A member 2, and cytochrome p450 family 2 subfamily B member 6. ^a*P* < 0.05 vs 0 μmol/L; ^b*P* < 0.01 vs 0 μmol/L; ^c*P* < 0.001 vs 0 μmol/L. ESR1: Estrogen receptor 1; EGFR: Epidermal growth factor receptor; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; MAPK14: Mitogen-activated protein kinase 14; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP2B6: Cytochrome P450 family 2 subfamily B member 6.

Curcumin exerts its effects through multiple mechanisms of action, thus, we analyzed KEGG pathways. The results indicated that curcumin prevents GC occurrence in a variety of ways. According to pathway analysis, the pathways most highly enriched in GC therapy with curcumin were correlated with the FOXO, P450 metabolic, GnRH, Toll receptor, cell cycle and epithelial cell signaling pathway. FOXO has been found to play a significant role in numerous cell processes, including proliferation, apoptosis, differentiation, stress reactions, and metabolic reactions[24]. Cytochrome P450 (CYP450) is a supergene family that activates carcinogens mainly through epoxidation, lightness, decalkylation, oxidation, and reduction[25]. Toll-like receptors (TLRs) can be used to specifically identify a variety of bacteria, viruses and other pathogenic microorganisms[26]. Recent research suggests a close association between *Helicobacter pylori* (*H. pylori*) infection-related gastric diseases and TLRs, with the expression of TLRs in gastric mucosal epithelial cells being

altered upon infection occurrence[27]. In summary, our study's findings indicate that curcumin could be a potent candidate for treating GC *via* multiple pathways. Despite this, further research is necessary to elucidate the precise mechanisms through which curcumin influences these pathways. This will not only enhance our understanding of curcumin's therapeutic potential but also provide insights into novel targets for the treatment of related conditions.

To elucidate the importance of this curcumin target, we constructed a PPI network. Through this network, we identified the first six hub targets, namely, *ESR1*, *EGFR*, *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6*. Survival analysis indicates that elevated levels of these genes are associated with poorer prognostic outcomes. To investigate the interaction mechanisms between curcumin and the six central molecules, we employed molecular docking methods. The results showed that curcumin has large binding sites for *ESR1*, *EGFR*, *CYP3A4*, *MAPK14*, *CYP1A2* and *CYP2B6*, with high binding scores, indicating good affinity for curcumin.

The genetic polymorphism of *CYP1A2* not only contributes to a certain extent to the increased risk of GC but particularly enhances the likelihood of developing GC in patients with *H. pylori* infection[28]. In addition, *CYP1A2* is a lipid metabolism-related gene. The biological process of lipid metabolism plays a dual role in regulating proliferation and migration of tumor cells, while also modulating the recruitment and function of tumor-infiltrating immune cells, thereby altering the immune microenvironment[29]. The genetic polymorphisms of various CYP450 enzymes have been thoroughly investigated for their roles in modulating the processes of cancer development[30]. Among these, *CYP3A4* is widely expressed in hepatocellular carcinoma, breast cancer, lung cancer, prostate cancer, and GC[31,32]. Additionally, microarray analysis has detected that enhanced expression of *CYP3A4* correlates closely with the therapeutic response of metastatic GC to chemotherapy[30]. The expression of *ESR1* is associated with fine T staging but has no significant correlation with N staging, suggesting that the estrogen receptor may promote local invasion of GC without affecting its lymph node metastasis mechanism. Estrogen receptor expression may be associated with age, sex, and other factors that promote the development of GC[33]. *MAPK14* is one of four p38 MAPKs. Passos *et al*[34] reported that the activation of the *MAPK14*/TGF signaling pathway leads to enhanced ROS activation, which participates in aging caused by DNA damage or telomere dysfunction[34,35]. Research has demonstrated that *MAPK14* exhibits high expression levels in tumor tissue and in radiotherapy-resistant GC cell lines. High *MAPK14* expression mediates radiotherapy resistance in GC by inhibiting apoptosis and affecting the redistribution of the cell cycle. Furthermore, *MAPK14* may serve as a predictive marker for radiation sensitivity in patients with advanced GC[36]. CYP is a carcinogen activator enzyme that includes *CYP3A4*, *CYP1A2* and *CYP2B6*, and the activities of these enzymes have the potential to activate the carcinogen, increasing cancer risk[37]. The pathogenesis of various cancers is closely associated with *EGFR*. Through the regulation of biological processes such as cell proliferation, survival, and metastasis, *EGFR* exerts a profound influence on tumor development and progression[38]. Preclinical study data indicate that *EGFR* is capable of sustaining tumor growth and development[39]. *EGFR* overexpression or constitutive activation is common in tumor cells and is associated with their proliferation, migration, and invasion, making *EGFR* an important target for anticancer therapy[40].

In this study, we have used CCK-8 to verify that significant inhibitory effect of curcumin on the proliferation of BGC-823 cells, and a qRT-PCR assay was used to verify that curcumin markedly influenced the hub targets *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6* at the gene level, as determined by network pharmacology. The effect of curcumin on *EGFR* expression exhibits dose-dependency, and curcumin slightly promoted the expression of *ESR1*. In summary, *ESR1*, *EGFR*, *CYP3A4*, *MAPK14*, *CYP1A2*, and *CYP2B6* play key roles in the pathogenesis of GC, indicating that curcumin could have a strong therapeutic effect on GC through these target genes. However, further biological experimental validation is required to determine the exact mechanism of curcumin in GC treatment.

CONCLUSION

Curcumin, a compound extracted from certain plants, exhibits anti-inflammatory, antitumor, and antioxidant properties, making it a potential treatment for GC. Its anticancer mechanisms involve transcriptional regulation, arrest of the cell cycle, and induction of apoptosis. Despite the efficacy of curcumin in inhibiting cell proliferation and inducing apoptosis, the precise underlying molecular mechanisms remain elusive. Notably, we discuss the cancer risk for polymorphisms of *CYP1A2* and the function of CYP450 enzymes. Biological validation demonstrated the inhibitory effect of curcumin on BGC-823 cell proliferation and its impact on hub target gene expression. In summary, curcumin holds promise for GC treatment through the modulation of key molecular targets, warranting further experimental validation. Our current study provides new insight into the mechanism of action of curcumin against GC.

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FOOTNOTES

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