BIOCELL
2023 47(5): 977-989

Tech Science Press

Network pharmacology and molecular docking identify mechanisms of medicinal plant-derived 1,2,3,4,6-penta-O-galloyl-beta-D-glucose treating gastric cancer

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Key words: 1,2,3,4,6-penta-O-galloyl-beta-D-glucose, Gastric cancer, Network pharmacology, Molecular docking, MAPK14, BCL2L1, VEGFA

Abstract: Background: 1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) is a natural polyphenolic compound derived from multiple medicinal plants with favorable anticancer activity. **Methods:** In this study, the mechanisms of PGG against gastric cancer were explored through network pharmacology and molecular docking. First, the targets of PGG were searched in the Herbal Ingredients' Targets (HIT), Similarity Ensemble Approach (SEA), and Super-PRED databases. The potential targets related to gastric cancer were predicted from the Human Gene Database (GeneCards) and DisGeNET databases. The intersecting targets of PGG and gastric cancer were obtained by Venn diagram and then subjected to protein-protein interaction analysis to screen hub targets. Functional and pathway enrichment of hub targets were analyzed through Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway databases. The differential expression and survival analysis of hub targets in gastric cancer were performed based on The Cancer Genome Atlas database. Finally, the affinity of PGG with hub targets was visualized by molecular docking. **Results:** Three hub targets were screened, including mitogen-activated protein kinase 14 (MAPK14), BCL2 like 1 (BCL2L1), and vascular endothelial growth factor A (VEGFA). MAPK14 had a higher expression, while BCL2L1 and VEGFA had lower expression in gastric cancer than in normal conditions. Enrichment analysis indicated enrichment of these hub targets in MAPK, neurotrophin, programmed death-ligand 1 (PD-L1) checkpoint, phosphatidylinositol 3-kinases/protein kinase B (PI3K-Akt), Ras, and hypoxia-inducible factor-1 (HIF-1) signaling pathways. **Conclusion:** Therefore, network pharmacology and molecular docking analyses revealed that PGG exerts a therapeutic efficacy on gastric cancer by multiple targets (MAPK14, BCL2L1, and VEGFA) and pathways (MAPK, PD-L1 checkpoint, PI3K-Akt, Ras, and HIF-1 pathways).

Introduction

Gastric cancer is a malignancy, which leads to high motility, and is the third leading cause of cancer-related deaths globally (Ajani *et al.*, 2022). More than 1 million people are newly diagnosed with gastric cancer each year worldwide (Thrift and El-Serag, 2020), and the overall survival for cancer of the stomach remains at 25% (Sexton *et al.*, 2020). In 2020, the new cases of gastric cancer reached approximately 480,000 in China, accounting for nearly 44% of all global new gastric cancer cases (Sung *et al.*, 2021). Risk factors for gastric cancer mainly include *Helicobacter pylori* infection, age, high salt intake, and diets low in fruit and vegetables (Smyth *et al.*, 2020). The incidence rate of gastric cancer rises progressively with age, and the median age at diagnosis is 70 years (Machlowska *et al.*, 2020). Most of the time, patients with gastric cancer are diagnosed at advanced stages, causing a poor prognosis (Ouyang *et al.*, 2022). Conventional therapies, including chemotherapy and resection, have limited clinical benefit; the median overall

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Received: 16 December 2022; Accepted: 17 January 2023

Doi: 10.32604/biocell.2023.028402

survival for patients with advanced-stage gastric cancer is approximately 8 months (Li *et al.*, 2021). The commonly used chemotherapeutic drugs, including fluorouracil, capecitabine, and platinum, exhibit high toxicity, resulting in low overall survival of gastric cancer (Li *et al.*, 2021; Shitara, 2017; Solomon and Garrido-Laguna, 2018). Recently, due to their low toxicity, traditional Chinese herbal medicines have attracted accumulating attention to treat gastric cancer as an adjunctive therapy (Wang *et al.*, 2021; Xu *et al.*, 2022).

1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) is a natural polyphenolic compound derived from multiple medicinal plants, including *Galla rhois*, *Schinus terebinthifolius*, *Rhus chinensis* Mill., *Paeonia lactiflora* Pall., etc., (Kant *et al.*, 2020). PGG is reportedly extracted from *P. lactiflora* Pall. Root and *G. rhois*, which showed favorable anti-inflammatory and antiviral activity (Kim *et al.*, 2020; Lee *et al.*, 2021). PGG possesses various biological and pharmacologic activities, including anti-cancer, anti-oxidative, anti-inflammatory, anti-coagulation, anti-angiogenesis, radio-protective, and neuroprotective properties (Zhang *et al.*, 2009). PGG has shown enormous potential as an anti-cancer agent. For example, PGG confers cytoprotection against oxidative damage in human hepatoma cells (Pae *et al.*, 2006). Oral administration of PGG can repress tumor growth and metastasis of triple-negative breast cancer (Lee *et al.*, 2011). PGG exerts anti-colorectal cancer effects by inducing apoptosis and tumor suppression (Kawk *et al.*, 2018). PGG also exerts anti-proliferative and anti-metastatic effects on colorectal cancer (Yang *et al.*, 2022). Also, PGG might exert its anti-cancer activity through autophagy-mediated senescence (Dong *et al.*, 2014). However, the potential therapeutic efficacy and pharmacological mechanisms of PGG on gastric cancer remain ambiguous.

Network pharmacology is a systemic approach that predicts the interactions between herbal components and targets for the treatment of diseases (Sharma *et al.*, 2022a, 2022b). Through network pharmacology, the potential molecular mechanisms for herbal drugs treating diseases are explored, contributing to the improvement of therapeutic strategies and the success rate of clinical trials (Li and Zhang, 2013). In this study, the underlying action mechanisms of PGG in the treatment of gastric cancer were explored using network pharmacology combined with molecular docking. Network pharmacology was applied to predict hub targets and signaling pathways of PGG for the treatment of gastric cancer. Subsequently, molecular docking was used to validate the interaction between PGG and hub targets. This research lays a solid foundation for the investigation of PGG as an adjuvant therapeutic drug for gastric cancer.

Methods

Prediction of 1,2,3,4,6-penta-O-galloyl-beta-D-glucose and gastric cancer-related targets

Pharmacological targets of PGG were retrieved from online tools, including the Herbal Ingredients' Targets (HIT) platform (v2.0; http://hit2.badd-cao.net/) (Yan *et al.*, 2022), the Similarity ensemble approach (SEA) dataset (https://sea.bkslab.org/) (Keiser *et al.*, 2007), and Super-PRED (https://prediction.charite.de/) (Nickel *et al.*, 2014). The PubChem ID of PGG was searched as 65238 from HIT. Based on its SMILES structure, PGG-related targets were predicted using SEA and Super-PRED databases. Gastric cancer-related targets were searched from the Human Gene Database (GeneCards v3; https://www.genecards.org/) (Safran *et al.*, 2010) and DisGeNET databases (http://www.disgenet.org/) (Piñero *et al.*, 2020) with the key word of "gastric cancer." Then, the PGG and cancer-related targets were mapped in the VennDiagram package (v1.7.3) (Chen and Boutros, 2011) to obtain overlapping targets. Finally, the interaction network between overlapping targets and PGG was visualized by Cytoscape 3.7.1 software.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses

The clusterProfiler package (v4.4.2) (Yu *et al.*, 2012) was utilized to analyze the GO function and KEGG pathway enrichment of overlapping targets of PGG and gastric cancer. GO functions include biological processes (BP), cellular components (CC), and 41 molecular functions (MF). The correlation between targets and GO/KEGG terms was evaluated by the hypergeometric distribution model as follows:

$$P = 1 - \sum_{i=0}^{k-1} \frac{\binom{M}{i}\binom{N-M}{n-i}}{\binom{N}{n}}$$

In this model, N represents the total number of genes, M represents the number of annotated genes in GO/KEGG, n represents the imported target genes, and k represents the number of shared genes. p-value < 0.01 represents the significant correlation between targets and GO/KEGG terms.

Protein-protein interaction (PPI) network

To obtain the hub targets of PGG treating gastric cancer, the overlapping targets were imported into the STRING platform (https://string-db.org/) (Szklarczyk *et al.*, 2021) to construct the PPI network. The protein type was set as *Homo sapiens*, and the confidence was set to more than 0.4. Results from SRTING were imported into Cytoscape 3.7.1 software for visualization. The top 10 target proteins in this network were ranked by the maximum neighborhood component (MNC), maximal clique centrality (MCC), and edge percolated component (EPC) methods using the cytoHubba plug-in (Chin *et al.*, 2014). VennDiagram package (v1.7.3) (Chen and Boutros, 2011) was used to obtain the intersection targets of MNC, MCC, and EPC analyses, and the intersection targets were considered hub targets.

Identification of hub targets

The transcriptome data of The Cancer Genome Atlas (TCGA)-gastric cancer were downloaded from the UCSC Xena database (https://xenabrowser.net/hub/). Differential expression of hub target genes in normal and tumor samples were analyzed by *t*-test. The interaction network

between differentially expressed genes (DEGs) and KEGG pathways was visualized in Cytoscape 3.7.1. In addition, to evaluate the prognostic effect of DEGs on gastric cancer, multivariate Cox regression analysis was performed to establish a prognostic model and calculate risk scores. From TCGA, patients with gastric cancer were divided into high- and low-risk groups, and survival analysis was carried out for the validation of the prognostic model.

Molecular docking

Molecular docking was performed for PGG and hub target proteins. The 3D protein structures of hub targets were downloaded from the RCSB protein data bank (RCSB PDB, http://www.pdb.org/) and ZINC database (https://zinc.docking.org/). The structure of PGG (CID_65238) was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/#query=65238). The Autodock Vina (v1.5.6) and PyMOL (v2.3.0) were applied for molecular docking (Seeliger and de Groot, 2010). The binding activity was assessed according to the free bind energy <−5.0 kcal/mol and hydrogen bond formation between the acceptor ligands.

Results

Identification of intersection targets of 1,2,3,4,6-penta-O-galloyl-beta-D-glucose against gastric cancer

Web-accessible databases, including HIT, SEA, and SuperPRED were used to predict the pharmacological targets of PGG. After the depletion of repetitive genes, 223 PGG-related targets were obtained (Suppl. Table S1). Meanwhile, 5627 gastric cancer-associated targets were collected from the GeneCards and DisGeNET databases (Suppl. Table S2). Venn diagram identified 141 intersection targets of PGG against gastric cancer (Fig. 1A). The network of PGG acting on 141 targets is presented in Fig. 1B.

Gene ontology and kyoto encyclopedia of genes and genomes enrichment analyses

The 141 intersection targets of PGG against gastric cancer were subjected to GO and KEGG enrichment analyses. In GO analysis, these targets were enriched in 777 BPs, 26 CCs, and 41 MFs. Results indicated that PGG mainly affected the regulation of body fluid levels (GO-BP), cytoplasmic vesicle lumen (GO-CC), and serine/threonine/

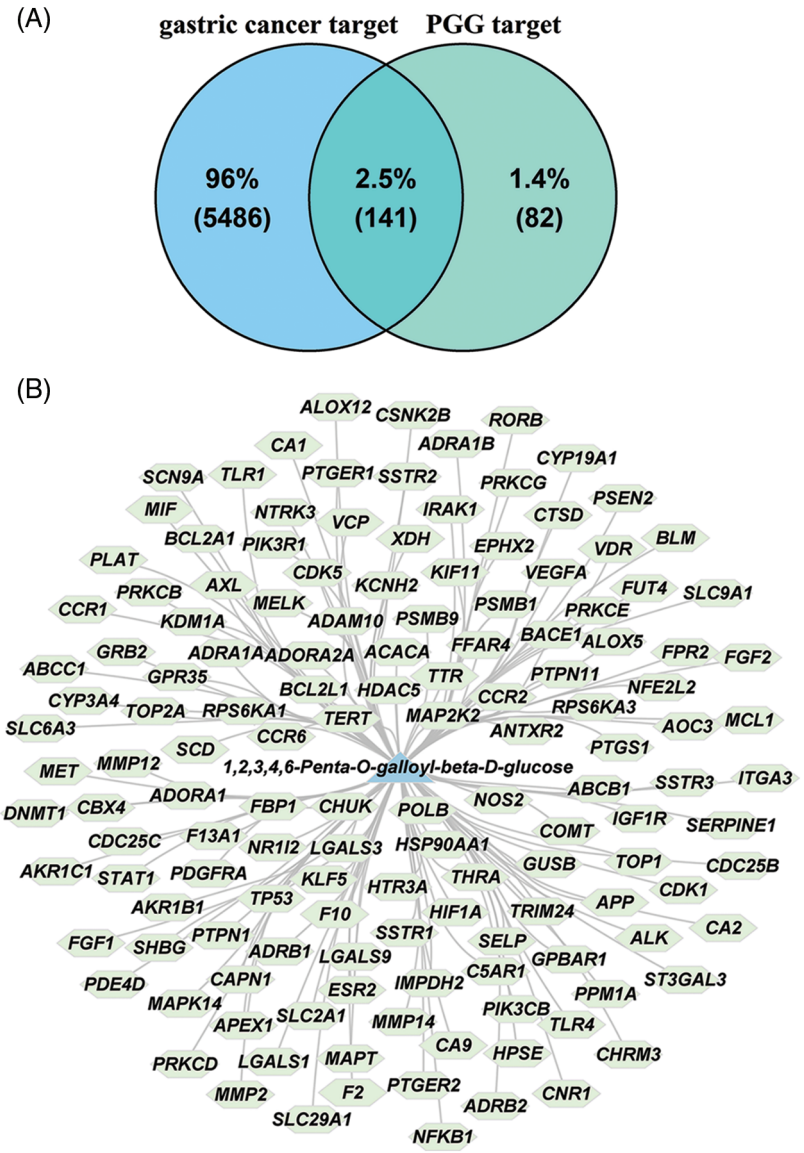

FIGURE 1. The intersection targets of 1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) against gastric cancer. (A) The intersection targets of PGG and gastric cancer are shown by a Venn diagram. (B) Compound-target network of PGG and 141 intersection targets.

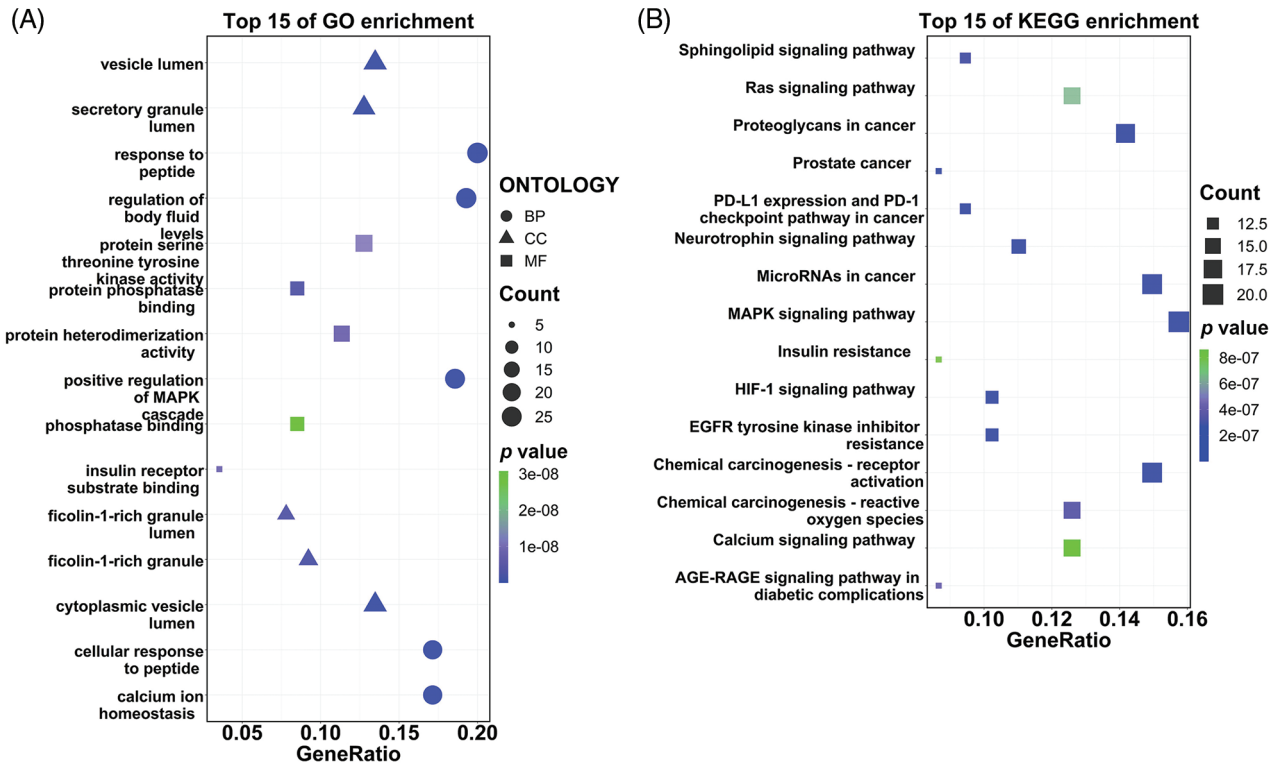

FIGURE 2. Gene Ontology (GO) function and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of 141 intersection targets. (A) Top 15 GO enrichment terms of targets, including biological process (BP), cellular component (CC), and molecular function (MF). (B) Top 15 KEGG enrichment pathways of targets.

tyrosine kinase activity (GO-MF) (Fig. 2A; Table 1). KEGG enrichment analysis showed that these intersection targets were associated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance, chemical carcinogenesis-receptor activation, proteoglycans in cancer, neurotrophin, programmed death-ligand 1 (PD-L1) expression and PD-1 checkpoint, hypoxia-inducible factor-1 (HIF-1), mitogen-activated protein kinase (MAPK), sphingolipid, Ras, and calcium-related signaling pathways (Fig. 2B; Table 2).

Protein-protein interaction network and hub targets for 1,2,3,4,6-penta-O-galloyl-beta-D-glucose against gastric cancer

PPI network for 141 intersection targets was established to identify hub targets of PGG against gastric cancer (Fig. 3A). In order to find hub targets from this PPI network, network scoring methods (MNC, MCC, and EPC) in cytoHubba were used to identify top 10 hub targets and construct sub-networks. In the MNC method, HIF1A, fibroblast growth factor 2 (FGF2), toll-like receptor 4 (TLR4), BCL2-like 1 (BCL2L1), tumor protein p53 (TP53), MAPK1, MAPK14,

TABLE 1

Top 5 Gene Ontology (GO) terms of biological process (BP), cellular component (CC), and molecular function (MF)

Ontology	ID	Description	*p*-value	Gene ID	Count
BP	GO:0050878	Regulation of body fluid levels	5.65E-19	MET/VEGFA/HIF1A/TLR4/HPSE/SERPINE1/MAPK14/NFE2L2/VDR/XDH/AXL/F2/ALOX12/PRKCD/PIK3CB/PLAT/CHRM3/SLC29A1/SLC6A3/PDGFRA/F10/ADORA1/PRKCE/F13A1/ADORA2A/SELP/AKR1B1	27
BP	GO:1901652	Rresponse to peptide	3.29E-17	TP53/MMP2/TLR4/ABCC1/PTPN11/SLC2A1/NFKB1/IGF1R/MAPK14/APEX1/NFE2L2/PTPN1/MMP12/GRB2/CDK5/STAT1/PRKCD/SLC9A1/PLAT/FBP1/PIK3R1/CA2/ADRB2/BACE1/PRKCB/FPR2/APP/HDAC5	28
BP	GO:1901653	Cellular response to peptide	2.49E-16	TP53/TLR4/ABCC1/PTPN11/NFKB1/IGF1R/APEX1/NFE2L2/PTPN1/GRB2/CDK5/STAT1/PRKCD/SLC9A1/PLAT/FBP1/PIK3R1/CA2/ADRB2/BACE1/PRKCB/FPR2/APP/HDAC5	24
BP	GO:0043410	Positive regulation of MAPK cascade	3.00E-15	VEGFA/TLR4/PTPN11/IGF1R/MIF/FGF2/PTPN1/XDH/LGALS9/C5AR1/GPBAR1/CCR1/FGF1/IRAK1/NTRK3/PDGFRA/FFAR4/	26

(Continued)

Table 1 (continued)

Ontology	ID	Description	*p*-value	Gene ID	Count
				MAP2K2/ADRB2/ADORA1/PRKCE/FPR2/ADRA1B/ALK/APP/ADRA1A	
BP	GO:0055074	Calcium ion homeostasis	7.95E-14	CNR1/FGF2/VDR/CCR2/C5AR1/PTGER2/F2/CDK5/CCR1/TRIM24/PDE4D/PIK3CB/CCR6/GPR35/PDGFRA/FFAR4/ADORA1/PRKCB/PRKCE/FPR2/ADRA1B/PTGER1/APP/ADRA1A	24
CC	GO:0060205	Cytoplasmic vesicle lumen	2.25E-12	VEGFA/HPSE/CTSD/HSP90AA1/NFKB1/SERPINE1/MAPK14/MIF/TTR/PRKCD/ALOX5/IMPDH2/BACE1/CSNK2B/F13A1/VCP/GUSB/APP/PSMB1	19
CC	GO:0031983	Vesicle lumen	2.50E-12	VEGFA/HPSE/CTSD/HSP90AA1/NFKB1/SERPINE1/MAPK14/MIF/TTR/PRKCD/ALOX5/IMPDH2/BACE1/CSNK2B/F13A1/VCP/GUSB/APP/PSMB1	19
CC	GO:0034774	Secretory granule lumen	1.87E-11	VEGFA/HPSE/CTSD/HSP90AA1/NFKB1/SERPINE1/MAPK14/MIF/TTR/PRKCD/ALOX5/IMPDH2/CSNK2B/F13A1/VCP/GUSB/APP/PSMB1	18
CC	GO:0101002	Ficolin-1-rich granule	8.56E-10	CTSD/HSP90AA1/MAPK14/LGALS3/MIF/ALOX5/IMPDH2/CAPN1/CSNK2B/FPR2/VCP/GUSB/PSMB1	13
CC	GO:1904813	Ficolin-1-rich granule lumen	1.53E-09	CTSD/HSP90AA1/MAPK14/MIF/ALOX5/IMPDH2/CAPN1/CSNK2B/VCP/GUSB/PSMB1	11
MF	GO:0019903	Protein phosphatase binding	1.52E-09	TP53/MET/MAPK14/LGALS3/PTPN1/GRB2/MAPT/STAT1/SLC9A1/PIK3R1/SLC6A3/VCP	12
MF	GO:0046982	Protein heterodimerization activity	5.49E-09	TP53/HIF1A/TOP2A/TLR4/MCL1/BCL2L1/ITGA3/CHUK/IRAK1/PIK3R1/AOC3/ADRB1/ADORA1/ADRA1B/BCL2A1/ADRA1A	16
MF	GO:0043560	Insulin receptor substrate binding	6.00E-09	IGF1R/GRB2/PRKCD/PIK3CB/PIK3R1	5
MF	GO:0004712	Protein serine/threonine/tyrosine kinase activity	9.28E-09	MET/CDK1/IGF1R/MAPK14/AXL/CDK5/MELK/PRKCD/RPS6KA1/RPS6KA3/IRAK1/NTRK3/PDGFRA/PRKCG/MAP2K2/PRKCB/PRKCE/ALK	18
MF	GO:0019902	Phosphatase binding	3.07E-08	TP53/MET/MAPK14/LGALS3/PTPN1/GRB2/MAPT/STAT1/SLC9A1/PIK3R1/SLC6A3/VCP	12

TABLE 2

Top 15 Kyoto Encyclopedia of Genes and Genomes enrichment analysis terms

ID	Description	Gene ratio	*p*-value	Gene ID	Count
the01521	EGFR tyrosine kinase inhibitor resistance	0.102362205	1.90E-10	MET/VEGFA/BCL2L1/IGF1R/FGF2/GRB2/AXL/PIK3CB/PIK3R1/PDGFRA/PRKCG/MAP2K2/PRKCB	13
hsa05207	Chemical carcinogenes–s-receptor activation	0.149606299	5.45E-10	VEGFA/HSP90AA1/NFKB1/KLF5/FGF2/ESR2/VDR/GRB2/RPS6KA1/PIK3CB/CYP3A4/RPS6KA3/PIK3R1/ADRB1/PRKCG/MAP2K2/ADRB2/PRKCB/EPHX2	19
hsa05205	Proteoglycans in cancer	0.141732283	2.26E-09	TP53/MMP2/MET/VEGFA/HIF1A/TLR4/HPSE/PTPN11/IGF1R/MAPK14/FGF2/GRB2/PIK3CB/SLC9A1/PIK3R1/PRKCG/MAP2K2/PRKCB	18
hsa04722	Neurotrophin signaling pathway	0.11023622	3.59E-09	TP53/PTPN11/NFKB1/MAPK14/GRB2/PRKCD/RPS6KA1/PIK3CB/RPS6KA3/IRAK1/PIK3R1/NTRK3/MAP2K2/PSEN2	14
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.094488189	1.04E-08	HIF1A/TLR4/PTPN11/NFKB1/MAPK14/STAT1/CHUK/PIK3CB/PIK3R1/MAP2K2/CSNK2B/ALK	12

(Continued)

Table 2 (continued)

ID	Description	Gene ratio	*p*-value	Gene ID	Count
hsa04066	HIF-1 signaling pathway	0.102362205	1.14E-08	VEGFA/HIF1A/TLR4/SLC2A1/NFKB1/IGF1R/NOS2/SERPINE1/PIK3CB/PIK3R1/PRKCG/MAP2K2/PRKCB	13
hsa04010	MAPK signaling pathway	0.157480315	2.26E-08	TP53/MET/VEGFA/NFKB1/IGF1R/MAPK14/FGF2/GRB2/CDC25B/MAPT/CHUK/FGF1/RPS6KA1/RPS6KA3/IRAK1/PPM1A/PDGFRA/PRKCG/MAP2K2/PRKCB	20
hsa05215	Prostate cancer	0.086614173	2.72E-07	TP53/HSP90AA1/NFKB1/IGF1R/GRB2/CHUK/PIK3CB/PLAT/PIK3R1/PDGFRA/MAP2K2	11
hsa05206	MicroRNAs in cancer	0.149606299	2.74E-07	TP53/MET/VEGFA/ABCB1/DNMT1/MCL1/ABCC1/NFKB1/GRB2/CDC25B/CDC25C/PIK3CB/PIK3R1/PDGFRA/PRKCG/MAP2K2/PRKCB/PRKCE/HDAC5	19
hsa04071	Sphingolipid signaling pathway	0.094488189	2.81E-07	TP53/ABCC1/CTSD/NFKB1/MAPK14/PIK3CB/PIK3R1/PRKCG/MAP2K2/ADORA1/PRKCB/PRKCE	12
hsa05208	Chemical carcinogenes–s-reactive oxygen species	0.125984252	3.19E-07	MET/VEGFA/HIF1A/PTPN11/NFKB1/MAPK14/NFE2L2/PTPN1/GRB2/CHUK/PRKCD/PIK3CB/PIK3R1/AKR1C1/MAP2K2/EPHX2	16
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.086614173	3.73E-07	MMP2/VEGFA/NFKB1/SERPINE1/MAPK14/STAT1/PRKCD/PIK3CB/PIK3R1/PRKCB/PRKCE	11
hsa04014	Ras signaling pathway	0.125984252	6.50E-07	MET/VEGFA/BCL2L1/PTPN11/NFKB1/IGF1R/FGF2/GRB2/CHUK/FGF1/PIK3CB/PIK3R1/PDGFRA/PRKCG/MAP2K2/PRKCB	16
hsa04931	Insulin resistance	0.086614173	8.18E-07	PTPN11/SLC2A1/NFKB1/PTPN1/PRKCD/RPS6KA1/PIK3CB/RPS6KA3/PIK3R1/PRKCB/PRKCE	11
hsa04020	Calcium signaling pathway	0.125984252	8.62E-07	MET/VEGFA/NOS2/FGF2/FGF1/NTRK3/CHRM3/PDGFRA/ADRB1/PRKCG/ADRB2/PRKCB/ADORA2A/ADRA1B/PTGER1/ADRA1A	16

vascular endothelial growth factor A (VEGFA), sirtuin 1 (SIRT1), and heat shock protein 90 alpha family class A member 1 (HSP90AA1) were top 10 hub targets (Fig. 3B). In the MCC method, top 10 targets were BCL2L1, HSP90AA1, protein tyrosine phosphatase non-receptor type 11 (PTPN11), TP53, MAPK1, MAPK14, VEGFA, insulin like growth factor 1 receptor (IGF1R), signal transducer and activator of transcription 1 (STAT1), and growth factor receptor bound protein 2 (GRB2) (Fig. 3B). In the EPC method, the top 10 targets were MAPK1, MAPK14, VEGFA, SIRT1, HSP90AA1, STAT1, HIF1A, TLR4, BCL2L1, and TP53 (Fig. 3B). We finally obtained six hub targets from Venn diagram displaying the intersection targets from MNC, MCC, and EPC sub-networks: TP53, VEGFA, MAPK1, HSP90AA1, MAPK14, and BCL2L1 (Fig. 3C).

Identification of hub targets in gastric cancer

Six hub targets were subjected to UCSC Xena to identify their differential expression in normal and tumor groups based on the TCGA-gastric cancer database. Results showed significantly upregulated levels of VEGFA, HSP90AA1, and BCL2L1 expression in tumor tissues ($p < 0.0001$). In contrast, MAPK14 expression was lower in tumor tissues than that in normal ($p < 0.05$; Fig. 4A). According to KEGG enrichment analysis, these four hub targets were mainly enriched in chemical carcinogenesis-receptor activation, EGFR tyrosine kinase inhibitor resistance, proteoglycans in cancer, MAPK, neurotrophin, and PD-L1 expression and PD-1 checkpoint-related signaling pathway (Fig. 4B). Subsequently, a prognostic model of four hub targets in gastric cancer was obtained by multivariate Cox regression analysis. Risk scores were calculated according to the prognostic model as follows: risk score = 2.2643 * MAPK14 −0.4435 * BCL2L1 + 4.5958 * HSP90AA1 + 0.1674 * VEGFA. Patients from the TCGA-gastric cancer database were categorized into high- and low-risk groups. Survival analysis displayed a lower survival probability for the high-risk group than the low-risk group ($p = 0.011$; Fig. 4C).

Molecular docking of 1,2,3,4,6-penta-O-galloyl-beta-D-glucose with hub targets

theThe interaction between PGG and four hub targets (MAPK14, BCL2L1, HSP90AA1, and VEGFA) was identified by molecular docking. Results showed that PGG could bind to MAPK14, BCL2L1, and VEGFA with the free binding energy of −8.3, −7.6, and −6.7 kcal/mol, respectively (Fig. 5; Table 3).

Discussion

Gastric cancer is a disease of global concern with poor prognosis and high mortality (Smyth *et al.*, 2020). Chemotherapy is a conventional therapy for advanced

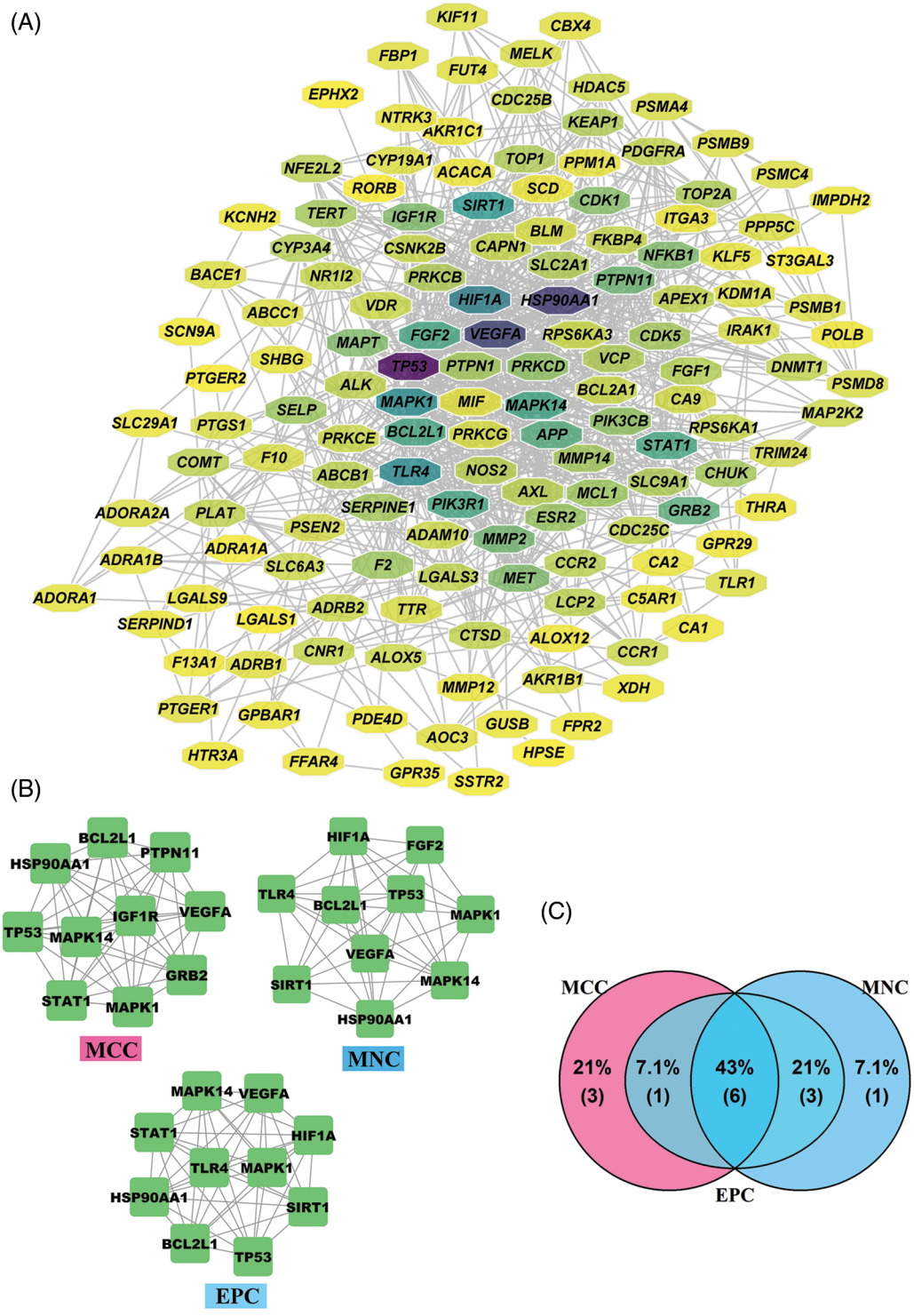

FIGURE 3. Identification of hub targets for 1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) against gastric cancer. (A) Protein-protein interaction (PPI) network of 141 intersection targets. (B) PPI networks of top 10 hub targets based on the maximum neighborhood component (MNC), maximal clique centrality (MCC), and edge percolated component (EPC) methods. (C) The intersection hub targets based on the MCC, MNC, and EPC methods were screened by a Venn diagram.

gastric cancer; however, the toxicity of chemotherapeutic drugs results in low median survival, often of less than one year (Smyth *et al.*, 2020). Traditional Chinese medicines (TCM) can reportedly potentiate the sensitivity to chemotherapeutic agents and exert the tumor-suppressing effect (Zhang *et al.*, 2020). In China, approximately 70% of patients with cancers were reported to benefit from TCM treatment (Zhang *et al.*, 2020). PGG, a natural polyphenolic compound from various medicinal plants, possesses favorable anti-tumor effects in multiple cancers, such as colorectal, lung, and breast cancers (Kim *et al.*, 2022; Xiang *et al.*, 2019; Yang *et al.*, 2022). However, the potential effects and molecular mechanisms of action of PGG in the treatment of gastric cancer remain to be determined.

In the current study, 141 potential targets of PGG were predicted for treating gastric cancer. These potential targets were analyzed by the PPI network, and six hub targets were obtained by MNC, MCC, and EPC methods. The six identified hub targets were TP53, VEGFA, MAPK1, HSP90AA1, MAPK14, and BCL2L1. TP53 is a tumor suppressor gene that regulates the expression of genes involved in the cell cycle, DNA repair, and metabolic

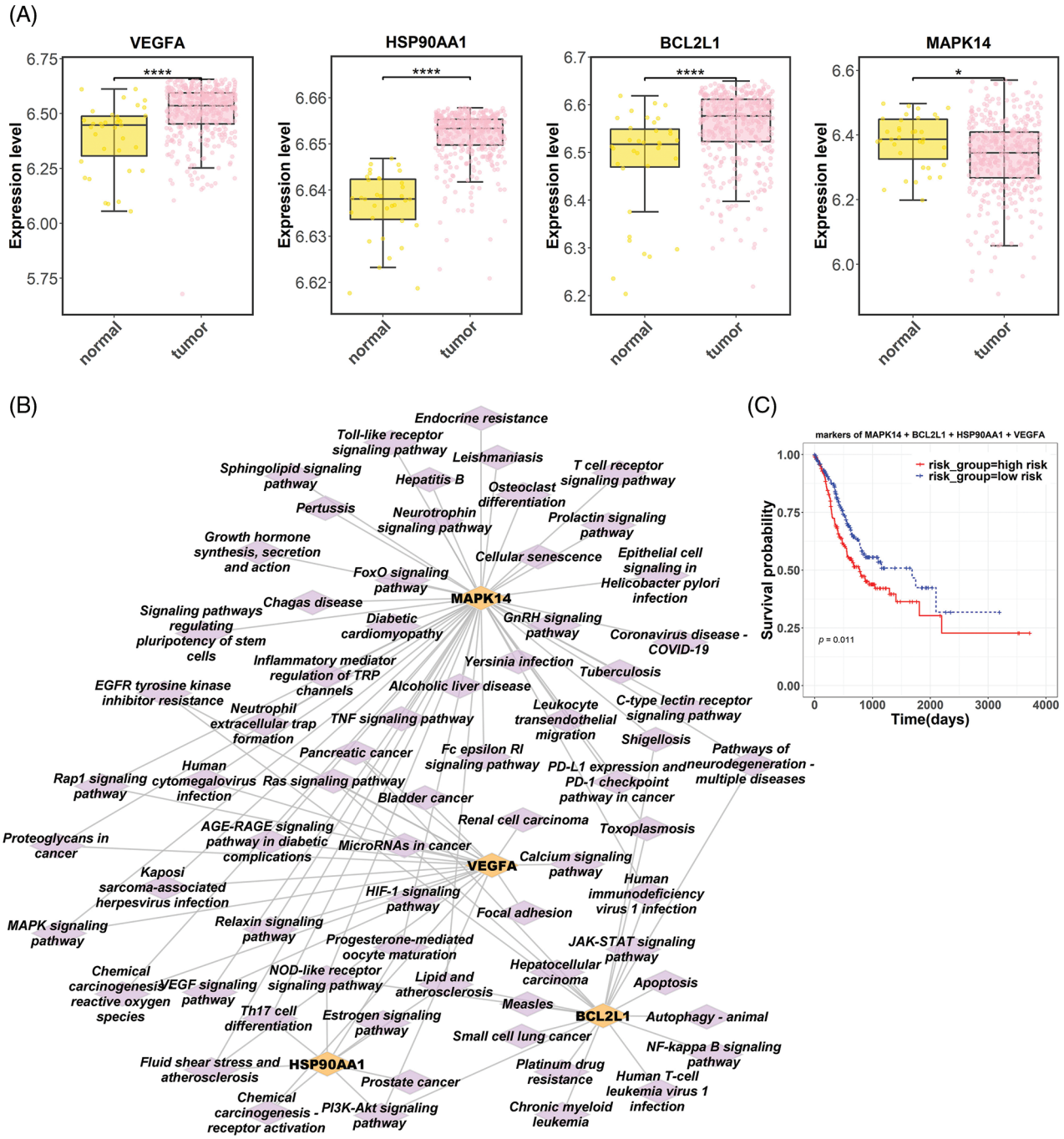

FIGURE 4. Bioinformatic analysis of hub targets in gastric cancer. (A) Differential expression of hub targets (VEGFA, HSP90AA1, BCL2L1, and MAPK14) in gastric cancer based on the Cancer Genome Atlas (TCGA) dataset. (B) The network of four hub targets and corresponding Kyoto Encyclopedia of Genes and Genomes pathways. (C) Survival analysis related to four hub targets in patients with gastric cancer (VEGFA, vascular endothelial growth factor A; HSP90AA1, heat shock protein 90 alpha family class A member 1; BCL2L1, BCL2 like 1; MAPK14, mitogen-activated protein kinase).

regulation (Donehower *et al.*, 2019). VEGFA is a major regulator of angiogenesis, implicated in tumor growth and metastasis in various cancers (Lu *et al.*, 2020). MAPK pathway is a classic cellular phosphorylation cascade, controlling cell proliferation, differentiation, inflammation, and metabolism in cancers (Jiang *et al.*, 2021). PGG reportedly alleviates inflammation and oxidative stress in diabetic nephropathy rats by inhibiting the MAPK/NF-κB signaling pathways (Wang *et al.*, 2022). HSP90AA1 reportedly acts as a diagnostic marker and therapeutic target for liver metastasis of gastric cancer (Chang *et al.*, 2009). BCL2L1 belongs to the BCL-2 family that regulates cancer cell apoptosis, tumor metastasis, and cell sensitivity to chemotherapeutic drugs (Warren *et al.*, 2019). The inhibition of Bcl-2/Bcl-xl has been a promising treatment strategy for gastric carcinoma by inducing apoptosis (Yi *et al.*, 2020). Summing up the above findings, PGG may inhibit cell proliferation and tumor metastasis of gastric cancer by targeting these hub genes.

Six hub targets were subjected to differential expression analysis in gastric cancer, and we found upregulated expressions of VEGFA, HSP90AA1, and BCL2L1, whereas

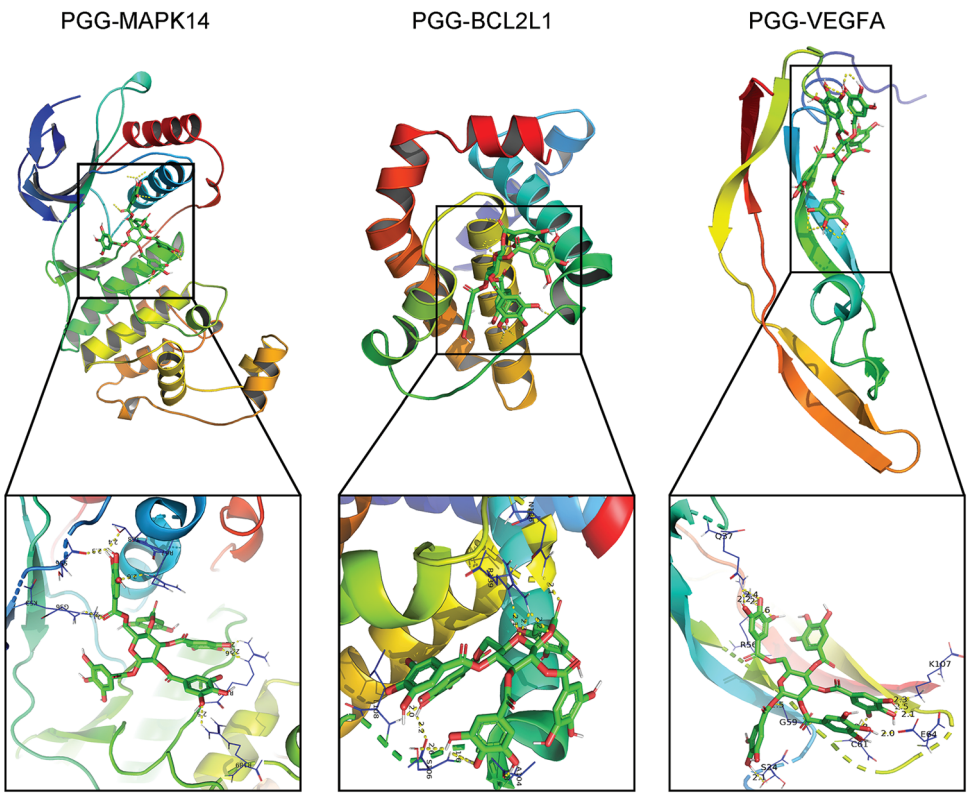

FIGURE 5. Molecular docking between 1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) and three hub targets (MAPK14, BCL2L1, and VEGFA).

TABLE 3

Molecular docking

Compound	Target	Free binding energy (kcal/mol)
1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG)	BCL2L1	−7.6
	MAPK14	−8.3
	VEGFA	−6.7

MAPK14 expression was downregulated in gastric cancer. GO functional analysis showed that PGG treatment against gastric cancer mainly concentrated in response to peptide, cytoplasmic vesicle lumen, and protein serine/threonine/tyrosine kinase activity, positive regulation of MAPK. Molecular docking revealed that PGG has good binding activities with the hub targets MAPK14 (−8.3 kcal/mol), BCL2L1 (−7.6 kcal/mol), and VEGFA (−6.7 kcal/mol). KEGG analysis showed that MAPK14 is mainly enriched in MAPK, neurotrophin, and PD-L1 checkpoint signaling pathways, BCL2L1 is closely related to PI3K-Akt and Ras signaling pathways, and VEGFA is associated with HIF-1 and MAPK signaling pathways. Taken together, PGG may treat gastric cancer by acting on MAPK14, BCL2L1, and VEGFA to regulate MAPK, neurotrophin, PD-L1 checkpoint, PI3K-Akt, Ras, and HIF-1 signaling pathways.

MAPK signaling pathway is an essential ubiquitous signal transduction pathway, responsible for cellular communication and regulates cell functions, including proliferation, differentiation, and survival (Degirmenci *et al.*, 2020). During cancer treatment, the MAPK pathway modulates drug sensitivity and resistance (Lee *et al.*, 2020). In gastric cancer, the inactivation of the MAPK pathway inhibits the malignant biological behavior of cancer cells (Jiang *et al.*, 2021). Previous studies have confirmed that PGG exerts a regulatory effect on the MAPK pathway. For example, PGG suppresses the MAPK/NF-κB signaling pathway to alleviate inflammation and oxidative stress in diabetic nephropathy (Wang *et al.*, 2022). Also, PGG attenuates pro-inflammatory responses of microglial cells through MAPK signaling pathway (Mendonca *et al.*, 2018). MAPK14 is a remember of the MAPK pathway; its inhibition impairs cell proliferation and migration of gastric cancer (Mesquita *et al.*, 2020). MAPK14 could be a potential pharmacological target for gastric cancer. In addition, VEGFA is the most functional isoform of the VEGF family, which is overexpressed in various tumors, including gastric cancer, and correlates with poor prognosis from metastasis (Karaman *et al.*, 2018; Yu *et al.*, 2022). Consistently, we found that VEGF has higher expression in gastric tumor samples than in normal samples. Our prognostic model also showed that high expression of VEGFA has higher risk scores and lower survival probability in patients with gastric cancer. In this study, we found that the MAPK pathway is enriched by MAPK14 and VEGFA. Molecular docking showed that PGG has a good affinity with MAPK4 and VEGFA. Therefore, we speculated that PGG may target MAPK14 and VEGFA to regulate the MAPK pathway, thereby suppressing gastric cancer. VEGFA is also enriched in the HIF-1 pathway, a key signaling regulating tumor hypoxia (Li *et al.*, 2019). Under hypoxia conditions, HIF-1α signaling is activated and regulates cell metabolism, inflammation, and tumorigenesis, which has been a promising therapeutic target for gastric cancer (Li *et al.*,

2019). Of note, PGG reportedly alleviates pancreatic cancer cachexia by inhibiting HIF-1α (Yang *et al*., 2019a). Thus, PGG may act on VEGFA to regulate the HIF-1 pathway, thereby inhibiting gastric cancer.

Neurotrophins are nerve growth factors expressed in human cancers to trigger neurogenesis and stimulate tumor growth (Griffin *et al*., 2018). One previous study revealed the carcinogenic role of the brain-derived neurotrophic factor in gastric cancer (Esfandi *et al*., 2019). In addition, the immune checkpoint PD-1/PD-L1 signaling pathway is a critical target of immunotherapies for human cancers (Ai *et al*., 2020). PD-L1 represses anti-tumor immunity by binding to its receptor PD-1 and counteracting T cell-activating signals on activated T cells (Sun *et al*., 2018). Notably, PD-L1 expression positively correlates with tumor lymphocyte infiltration in gastric cancer (Wang *et al*., 2019). Our study found that PGG-targeted MAPK14 is related to neurotrophin and PD-L1 checkpoint pathways, implying the potential mechanisms of PGG against gastric cancer.

Another hub target BCL2L1 was found to be related to PI3K-Akt and Ras signaling pathways. The PI3K-Akt signaling pathway is an essential intracellular pathway that regulates cell proliferation, differentiation, metabolism, and response to extracellular stimulation (Noorolyai *et al*., 2019). Due to the key role of PI3K-Akt signaling in cellular processes, this pathway has emerged as a noteworthy target for cancer treatment (Yang *et al*., 2019b). Previous studies have reported the tumorigenic property of PI3K-Akt in gastric cancer (Rong *et al*., 2020; Wu *et al*., 2021). Our study revealed that PGG treating gastric cancer may be achieved by targeting BCL2L1 and regulating the PI3K-Akt signaling pathway. In addition, the Ras signaling pathway also plays a pivotal role in cellular processes, regulating cellular responses to growth factors and affecting cell proliferation, differentiation, migration, and apoptosis (Al Mahi and Ablain, 2022). Ras is the most frequently mutated gene in cancers; consequently, Ras-targeted therapy has been effectively developed for cancers (Moore *et al*., 2020). The inhibition of the Ras pathway contributes to stalling the development of gastric cancer and enhancing the efficacy of chemotherapy (Liao *et al*., 2021). Our study developed the potential therapeutic mechanism of PGG against gastric cancer, that is, the regulation of BCL2L1 and the Ras signaling pathway.

Conclusion

In the present study, the pharmacological mechanisms of PGG on gastric cancer were analyzed through network pharmacology and molecular docking. The potential anti-cancer targets and signaling pathways of PGG were predicted. We found that PGG may act on MAPK14, BCL2L1, and VEGFA to regulate MAPK, neurotrophin, PD-L1 checkpoint, PI3K-Akt, Ras, and HIF-1 signaling pathways, thereby restraining gastric cancer progression. However, *in vitro* and *in vivo* validation experiments were not included in this study. Therefore, in the follow-up study, we plan to design pharmacological experiments *in vitro* and *in vivo* to validate the mechanisms of PGG in treating gastric cancer. The present study provides an important foundation for the therapeutic application of PGG on gastric cancer.

Funding Statement: This research was supported by the Natural Science Foundation of Gansu Province [Grant Numbers 22JR5RA930, 22JR5RA894], the Talent Project of Lanzhou Science and Technology Bureau [Grant Number 2022-3-44], the projects managed by the Administration of Traditional Chinese Medicine [Grant Number GZKG-2022-54], and Intra Hospital Fund of the First Hospital of Lanzhou University [Grant Number ldyyyn2021101].

Author Contributions: The authors confirm contribution to the paper as follows: Study conception and design: Man Ren, Yuan Yang. Data collection: Nannan Zhao. Analysis and interpretation of results: Dan Li. Draft manuscript preparation: Man Ren. Manuscript review and edit: Yuping Wang, Yongning Zhou. Funding acquisition: Man Ren and Dan Li. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The data used to support the findings of this study are included within the article and can be made available upon request to the corresponding author.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

Supplementary Materials: The supplementary material is available online at DOI 10.32604/biocell.2023.028402.

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Supplementary Materials

TABLE S1: The 223 targets related to 1,2,3,4,6-penta-O-galloyl-beta-D-glucose

TABLE S2: The 5627 gastric cancer-associated targets were collected from the GeneCards and DisGeNET databases