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Original Research

A network pharmacology to explore the mechanism of cultured bezoar in vitro for the treatment of colorectal cancer

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Abstract

Objective: To analyze the molecular mechanism of in vitro culture of bezoar for the treatment of colorectal cancer patients by network pharmacology.

Method: The main components of bezoar were found using TCMSP, then the corresponding molecular formula was searched in PubChem, and the molecular formula of isomeric smile was copied. The isomeric smile molecule was simply placed in the Swiss Target Prediction database to make target prediction, the colorectal cancer disease related genes were screened out through Gebecards, and the target intersection integration between cultured bezoar and colorectal cancer was performed with VENNY. The protein-protein interaction network of intersecting targets was drawn using STRING database (confidence 0.09), and the pathway prediction and related literature research of gene targets for cancer treatment were obtained, and the embellish processing was performed in Cystoscope software. Target intersection was searched in Meta Scape database, KEGG pathway and go bioanalysis were performed, and the main therapeutic pathways of bezoar for colorectal cancer were found. SPSS2.0 statistical method was used to statistically treat the patients with colorectal cancer who had used in vitro cultured bezoar within one year.

Result: The main targets of cultured bezoar for the treatment of colorectal cancer are SRC, TP53, MAPK3, MAPK1, HSP90AA1, JUN, PIK3CA, PIK3R1, ESR1, MAPK14, EGFR, HDAC1, FYN, PTPN11, NR3C1, AR, JAK2, CDK1. IL6, MAPK8, JAK1, CDH1, MAP2K1, NCOA3, MDM2, ABL1, SIRT1, CDK2, TGFB1, SYK. The therapeutic pathways include SRC pathway, PI3K/Akt pathway, EGF/EGEF pathway, and RAS-RAF-MAPK pathway.

Conclusion: SRC pathway, PI3K/Akt and EGF/EGEF pathway can promote cell proliferation and inhibit cell apoptosis, and their applications in colorectal cancer have been widely accepted.

Keywords: Target Spot; Genes; Cultured bezoar in vitro; Colorectal cancer; Database; PI3K/Akt; MAPK; EGEF

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INTRODUCTION

Colorectal cancer represents approximately 10% of all diagnosed cancers and cancer-related deaths globally each year, ranking third in terms of incidence and second in terms of fatality rate[1,2]. Despite recent advancements in treatment and multidisciplinary care, patients with CRC continue to experience significant adverse events that impact prognosis and diminish quality of life[3,4]. Over 50% of CRC patients are diagnosed at an advanced stage with a 5-year survival rate of <14%[5,6]. Therefore, the development of alternative therapies with reduced toxicity is imperative for more effective clinical treatment and mitigation of adverse effects. As a significant complementary and alternative medicine, traditional Chinese medicine has demonstrated beneficial effects on cancer patients and gained widespread acceptance worldwide[7]. Previous studies have indicated that traditional Chinese medicine as an adjuvant therapy alongside chemotherapy or radiotherapy can enhance treatment efficacy, reduce adverse reactions, improve quality of life, and extend survival time. Due to its effectiveness and minimal side effects, it has gained increasing popularity in Western countries. With a medicinal history spanning over 2000 years in our country, bezoar was first documented in the Shennong Herbarium as

the dried gallstone from Bos taurus domesticus Gmelin[8]. Its bitter taste provides cooling properties while treating fever-induced dizziness, delirium, epilepsy convulsions in children, malnutrition swollen throat, mouth, and tongue sores, warts, and unculosis. Modern research has confirmed bezoar's antipyretic, cough expectorant anti-inflammatory antiviral, and anti-tumor pharmacological effects. Since the early 20th century[9],through extensive research by scholars both domestically and internationally, the chemical composition of bezoar has been largely elucidated, encompassing bile pigments (bilirubin and biliverdin),bile acids, cholesterols, fatty acids lecithin, mucin smooth muscle contractile substances amino acids carotenoids, oily cardiac components, inorganic components, and vitamin D. Heat-clearing and detoxifying Chinese medicines can enhance immunity and promote macrophage function thereby controlling tumor development to a certain extent[10]. Bezoar with its heat-clearing and detoxifying effects exerts therapeutic benefits on various tumors especially those affecting the digestive tract[11] as a substitute for natural bezoar artificial bezoar is nearly identical in terms of features structure composition efficacy and clinical outcomes. Studies have shown that cultured bezoar in vitro can induce apoptosis of human hepatoblastoma HepG2 cells and inhibit tumor growth[12].

Network pharmacology is a promising approach for elucidating the scientific basis and treatment mechanisms of traditional Chinese medicine prescriptions, as well as for discovering new drugs. With the rapid advancement of bioinformatics and pharmacology, network pharmacology comprehensively investigates the interrelationships among drugs, targets, and diseases, visually demonstrating drug-target-disease networks. This method effectively observes the impact of drugs on diseases[13], aligning with the theory of Chinese medicine that emphasizes synergistic effects. Moreover, network pharmacology enables the discovery of important bioactive compounds in Chinese medicine formulations[14]. In vitro cultured bezoar shares many similarities with natural bezoar and contains significant pharmacological effects on various systems and anti-inflammatory and antioxidant properties. To further elucidate the targeted therapeutic effect of in vitro cultured bezoar combined with traditional Chinese medicine on colorectal tumors, we employed network pharmacology to explore its mechanism of action precisely at molecular level.

METHODS

Database and analysis software

Construction of a chemical composition database for bezoar involved the use of various databases and analysis software, including TCMSP, Uni-prot, Gene card, STRING, PubChem, Swiss Target Prediction, PubMed, Cyto-scape 3.7.2 software and SPSS 23.0 statistical analysis software. software.

Construction of chemical composition database of bezoar

In the TCMSP database [Search criteria: oral bioavailability (OB) ≥30% and

According to the search result of drug-likeness (DL) ≥ 0.18], the active components of bezoar were identified as cholic acid, bilirubin, deoxycholic acid, cholesterol, hyodeoxycholic acid, taurine, methyl deoxycholic acid and valerate.

Prediction and screening of target of active ingredients of bezoar

Canonical SMILES of each active component of bezoar were searched in PubChem Compound-NCBI database. The target of each active component of bezoar was found in the Swiss target prediction database according to Canonical SMILES formula, and the composition-target interaction map was drawn. Find connections between various targets in the STRING database and plot protein-protein interactions

(Protein-protein interaction (PPI) diagram.

Colorectal cancer target screening

Targets were found in Dis GeNET Gene disease association database (search criteria: score-GDA > 0.01) and Gene Cards database (search criteria: relevance score≥10).

Target screening for composition-disease interactions

The target of interaction between various components of bezoar and colorectal cancer was summarized, and the target gene corresponding to the common target was identified in uniprot database.

Functional enrichment and pathway enrichment

The target of bezoar was imported into the DAVID database, the Select Identifier was set as OFFICIAL GENE SYMBOL, the List Type was set as Gene List, the species was limited to human, and the GO energy enrichment analysis was carried out for the target of bezoar. KEGG path enrichment analysis was performed using KEGG Mapper in KEGG database.

RESULTS

Main chemical components of bezoar were cultivated in vitro, and compound targets were collected

The chemical substances (methyl (4R) -4- [(3R, 5S, 7S, 8R, 9S, 10S, 12S, 13R, 14S, 17R) -3, 7, 12-- trihydroxyl --10, (Set parameters OB≥20%, DL≥0.1) of bezoar were sorted out using TCM pharmacology database and analysis platform (TCMSP). 13-- dimethyl -- 2,3,4,5,6,7,8,9,11,12,14,15,16,17 -- tetrahydro-1H -- cyclopentane [a] phenanthrene --17-- yl] valerate (MOL008838), deoxycholic acid methyl ester (MOL008839), deoxycholic acid (MOL008845), Oleanolic acid (MOL000263), biliverdin (MOL008843), and eoxycholic acid (MOL008842)), and the degree value of the above six components is 100 according to cytohubba plug-in. After the removal of duplicate values from all the targets, 333 targets of all the bezoar components were obtained, and 83 targets with greater than degree values were obtained by using cytohubba plug-in. The targets were shown in Table 1. Visibility values greater than 20 are TP53, MAPK3, MAPK1, SRC, RXRA, HSP90AA1, ESR1, PIK3R1, PIK3CA, CDK1, EGFR, HDAC1, MAPK14, JAK1, JAK2, PTPN11, MAPK8, JAK3. Among the targets, TP53 is a tumor

suppressor, and MAPK pathway is an important association factor of CRC, which affects cell proliferation, differentiation and apoptosis. JUN, SRC, PIK3CA are all related to CRC (Table 1).

Target collection in colorectal cancer and target integration with bezoar

In the search for "colorectal cancer" in Gene Cards, all relevant targets and uniprot ids are obtained, and a total of 1496 are classified after duplicate values are removed. The sorted colorectal cancer targets and bezoar targets were input into venny2.0 for mapping, 126 (7.3%) intersection targets were obtained, and the intersection targets of the two were copied. The obtained target was the target of bezoar acting on CRC (Figure 1).

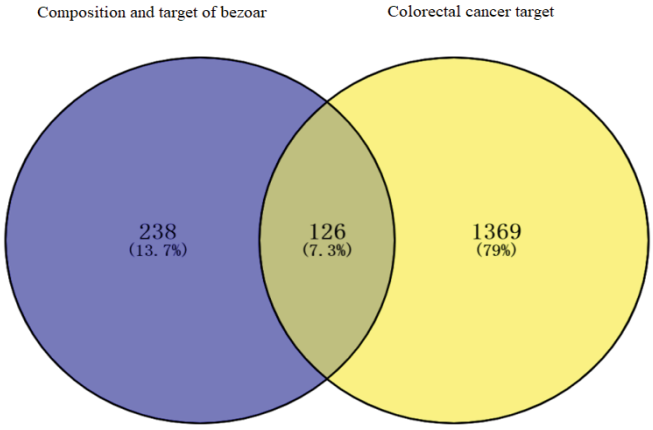

Figure 1. Composition of bezoar and colorectal cancer target

The intersection target of bezoar and colorectal cancer was identified as PPI network

The STRING database defined the species as human and obtained the PPI map. The dots represent all the proteins encoded by the gene; The lines represent interactions between proteins. The more concentrated and colorful the protein connections, the more important its role in the PPI network. Visibility values greater than 20 are TP53, MAPK3, MAPK1, SRC, RXRA, HSP90AA1, ESR1, PIK3R1, PIK3CA, CDK1, EGFR, HDAC1, MAPK14, JAK1, JAK2, PTPN11, MAPK8, JAK3. Among the targets, TP53 is a tumor suppressor, and MAPK pathway is an important association factor of CRC, which affects cell proliferation, differentiation and apoptosis, JUN, SRC, PIK3CA are all related to CRC (Figure 2).

Go enrichment analysis

Open the meta scape database, import the selected intersection target of colorectal cancer and in vitro cultured bozoa, select H.Sapens and click enrichment analyze, and select the KEGG signaling pathway and go enrichment analysis, respectively. The visualization results are as follows: The go enrichment analysis of protein-protein interaction has a total of 6,228 go biological processes, and the top ten are functional descriptions that retain the best scores of the three P-values. go biological processes are through protein phosphorylation, response to hormones, and functional descriptions. Processes such as protein serine/threonine/tyrosine kinase activity regulate colorectal cancer target genes for therapeutic purposes. And that several ways are respectively go0006468 go0009725, go0004712(Figure 3, Figure 4).

Enrichment analysis of KEGG signal pathway

According to the analysis results of KEGG, there are 249 KEGG

Figure 2. Intersection diagram of targets of bezoar and colorectal cancer

Table 1. Main chemical components of bezoar that greater than degree values

Gene id	Degree	Gene id	Degree	Gene id	Degree	Gene id	Degree
TP53	40	PPARA	16	PTPN2	10	PLA2G4A	8
MAPK3	38	MAP2K1	16	AURKA	10	PTGS1	8
MAPK1	37	RXRG	16	CDC45	10	CYP19A1	8
SRC	35	CDK2	16	HSP90AB1	10	CYP17A1	8
RXRA	34	MAPK11	15	AKR1C3	10	THRB	7
HSP90AA1	31	RARA	13	TGFB1	9	HSF1	7
ESR1	27	CDK4	13	MTOR	9	PARP1	7
PIK3R1	26	SYK	12	PRKCB	9	MMP2	7
PIK3CA	25	PTPN6	12	BCL2	9	PIK3CB	7
CDK1	24	NOS2	12	ALOX5	9	NR1H3	7
EGFR	24	CHEK1	12	CYP11B2	9	CDC25B	7
HDAC1	23	MDM2	12	CYP11B1	9	TYMS	7
MAPK14	23	RARG	11	IL6ST	8	KDM1A	7
JAK1	22	RARB	11	NR0B2	8	MAPK9	7
JAK2	22	KDR	11	MMP9	8	CYP2C9	7
PTPN11	20	TNF	11	PTPN1	8	SRD5A2	7
MAPK8	20	SIRT1	11	TERT	8	HSD17B3	7
JAK3	20	GSK3B	11	AURKB	8	HSD17B2	7
NR3C1	19	PTGS2	11	TOP2A	8	APP	7
AR	17	PPARG	10	CDC25A	8	CPT1A	7
IL6	16	MET	10	EZH2	8		

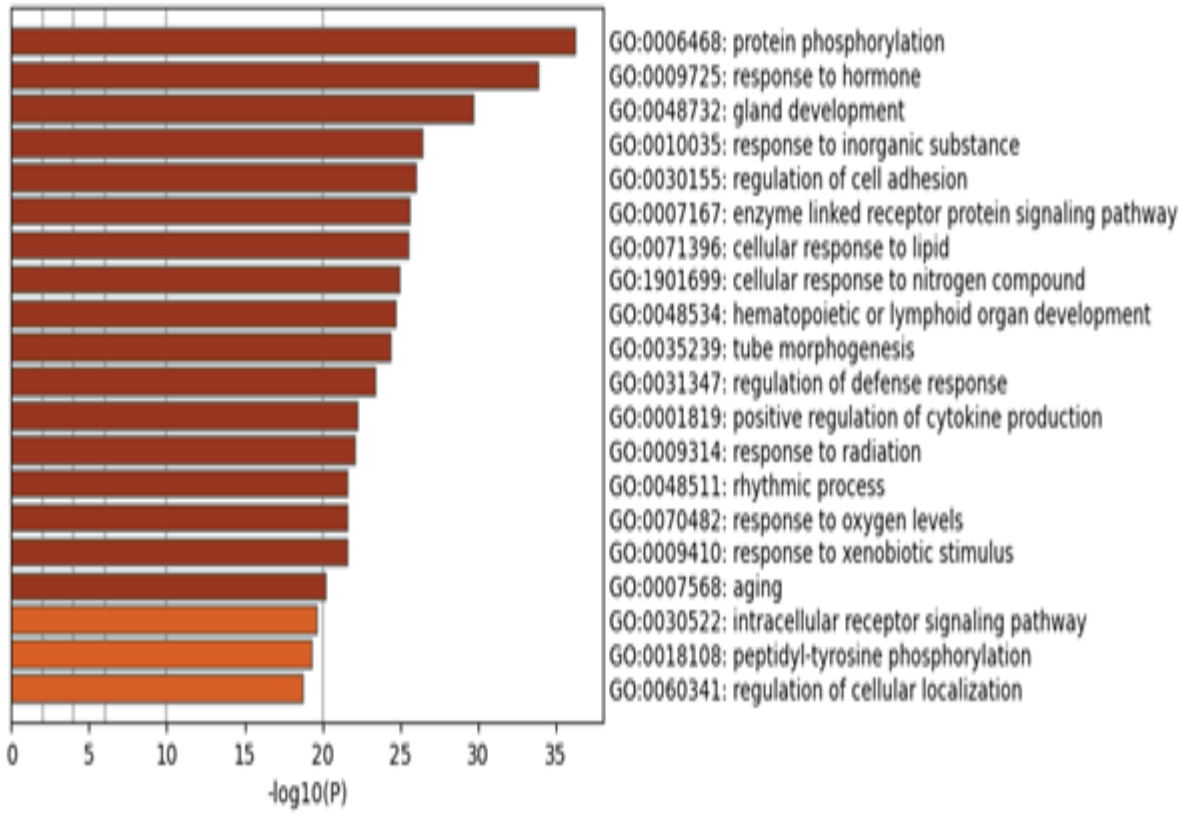

Figure 3. Results of GO/KEGG enrichment analysis

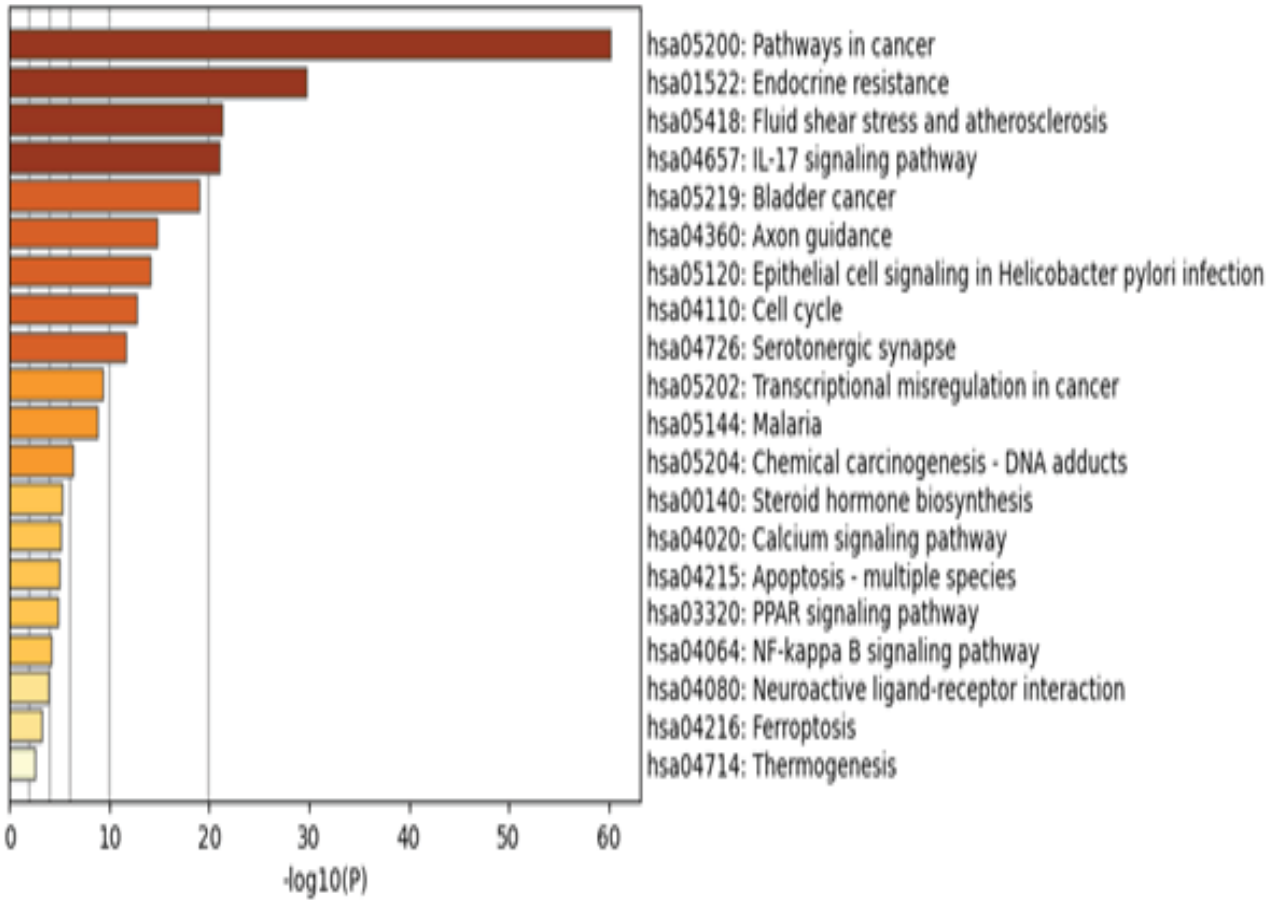

Figure 4. Go biological analysis results

pathways for the treatment of colorectal cancer by bezoar, and the three best P-value scoring pathways are cancer pathways, endocrine resistance, lipids and atherosclerosis. Including SRC, TP53, MAPK3, MAPK1, HSP90AA1, JUN, PIK3CA, PIK3R1, ESR1, MAPK14, EGFR, HDAC1, FYN, PTPN11, NR3C1, AR, JAK2, CDK1, IL6, MAPK8, JAK1, CDH1, MAP2K1, NCOA3, MDM2, ABL1, SIRT1, CDK2, TGFB1, SYK, etc. KEGG analysis revealed that bezoar is mediated by cancer pathways, endocrine resistance, protean can in cancer, P13K-Akt signaling pathway, and tumor necrosis factor signaling pathway. The main pathway processes also showed activation of MAPK kinases ERK1/2, JNK and p38, phosphorylation of MAPKS to phosphorize ATF-2, activation of SRC kinase ERK, and activation of PAR1(Figure 5).

DISCUSSION

The MAPK pathway was identified as one of the most significant genetic markers associated with CRC in a German genome-wide association study. MAPK signaling is characterized by sequential activation of kinases that regulate cell proliferation, differentiation, and apoptosis[15]. CRASG12C was the first KRAS mutation targeted by AMG 510 to induce a pro-inflammatory tumor microenvironment in mice with normal immune function, enhancing the efficacy of other anticancer drugs. It has also demonstrated antitumor activity in clinical trials. The BRAF gene encodes serine-threonine kinase, with the most common BRAF mutation being V600E. mCRC patients with BRAFV600E mutations have a poorer prognosis and more aggressive disease[16]. MAPK1/ERK2 and MAPK3/ERK1 play crucial roles in the MAPK/ERK cascade, participating in signal cascades initiated by activated KIT and KITLG/SCF. The MAPK/ERK cascade regulates cell growth, adhesion, survival, and differentiation through transcriptional regulation, translation control, and cytoskeletal rearrangement[17]. ERK1/2 inhibitors are effective for tumors with mutations in upstream targets of the MAPK pathway and for cancers with alterations in this pathway. Phosphorylation of ERK1/2 promotes cell proliferation. Inhibitors targeting upstream components of the ERK pathway exhibit excellent antitumor activity[18]. Ras small GTPase is frequently mutated in human cancer and activates the Raf-MEK-ERK pathway as an important downstream effector. B-Raf transmits signals from EGFR to KRAS[19]; over half of CRCs harbor mutations in either KRAS or B-Raf, promoting conduction along the MAPK signaling pathway while inhibiting cell death[20].

SRC is a non-receptor tyrosine kinase belonging to a family

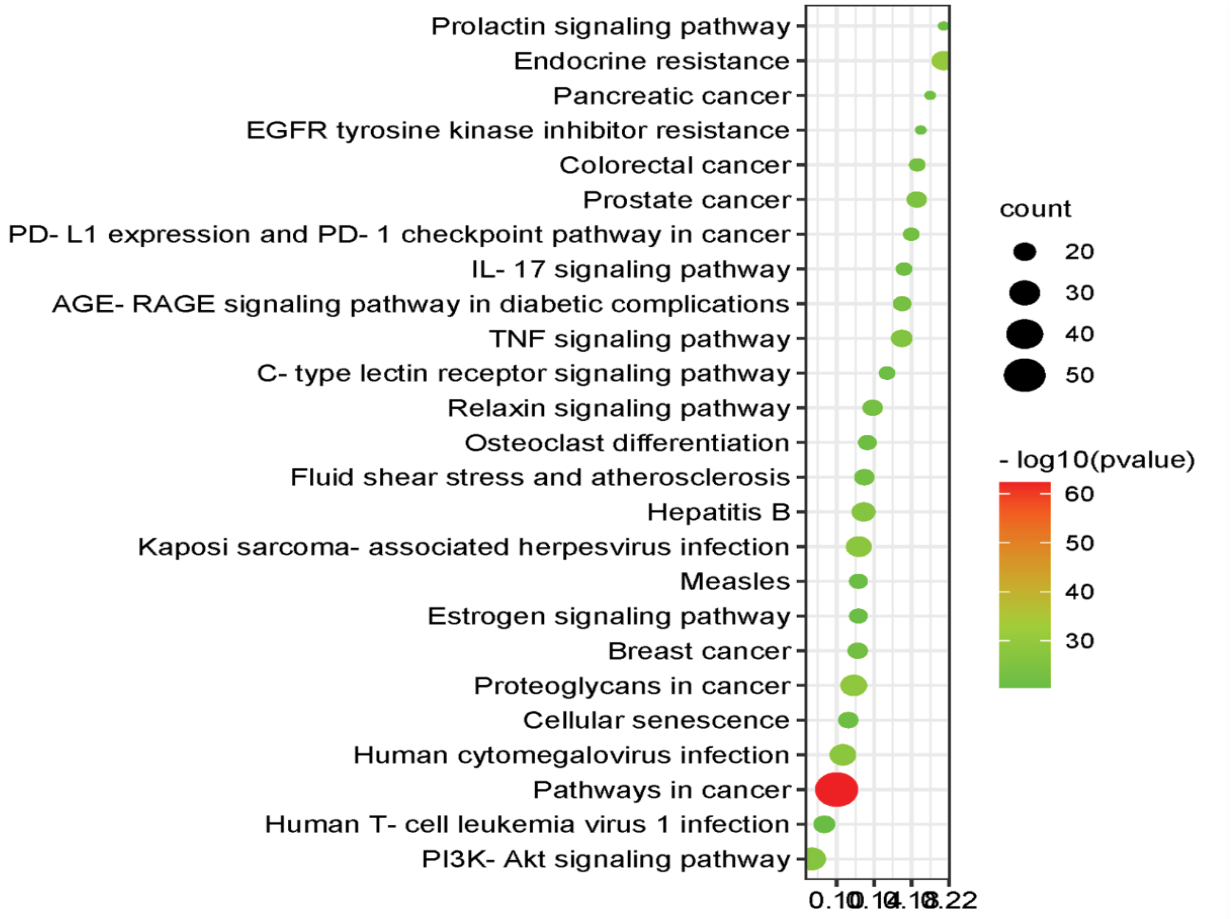

Figure 5. Bubble diagram analyzed by KEGG and GO

known as SRC family kinases (SFKs), which includes nine enzymes collectively identified as SFKSs. Activation of SFKS correlates with various membrane receptors, regulators, inhibitors that promote CRC cell proliferation metastasis chemical resistance formation cancer stem cells (CSC). SRC is activated by ligands complexes such EGF EGFR HGF c-MET VEGF VEGFR FGFR IL4 IL-13Rα2 IL6 IL-11 form signaling pathways Further activation downstream target signaling pathways AKT NF-***κB*** HO-1, MAPKERK and other cancer proteins enhances proliferation vascularization metastasis CRC cells addition GPCRs activate SRC-mediated signaling pathways involved progression CRC[21]. PGE2/EP1, PEG, and CCK2R activate the EGFR/SRC/MAPK/ERK, HIF-1α/SRC/AKT/VEGF signaling axis, thereby promoting cell proliferation[22]. Additionally, SRC-induced Rac1 activates WNT-β-catenin signaling to enhance reactive oxygen species (ROS) production, leading to increased migration of CRC cells[23]. AHR is activated by the ligand TCDD and directly interacts as a transcription factor to promote SRC expression. SRC-mediated EGFR activation stimulates COX2 and ERK1/2 to facilitate CRC cell proliferation. The degradation of ERK1/2 mediated by SRC inhibits the apoptosis of CRC cells through the inhibition of death accelerator Bik[24]. The pI3K/Akt signaling pathway plays a crucial role in cancer cell proliferation and differentiation. Src and EGFR regulate RTK signals which are transmitted to PI3K, Akt, signal transduction, and transcriptional activator 3 (STAT3) to promote cell growth in colorectal cancer[25]. TP53 is a tumor suppressor gene that induces apoptosis, increases DNA repair protein levels, maintains genome stability and inhibits cancer progression. Common activation of the PI3K gene in CRC along with PTEN inactivation leads to Akt expression and downstream target promotion for enhanced cell growth and apoptosis resistance. Therefore, PI3K/Akt inhibition has been widely used for treating CRC. EGF binding to EGFR activates EGER which then triggers the PI3K/Akt pathway ultimately promoting tumor proliferation[26]. JUN is a key gene in the AP-1 family of transcription factor complexes. MiR-22 acts as an important cancer-suppressing miRNA that inhibits AP-1's ability to bind DNA. Jun down-regulates p53 and TP53 expression while p53 activates miR-22 expression. Oncogene overexpression makes c-jun (JUN) easily bind CCND1 activating cyclin D1 for promoting abnormal colorectal cancer cell proliferation via Cell division cycle associated protein 2 targeting CCND1 through the PI3k/Akt pathway stimulation IGF-I serves as an important anti-apoptotic factor in CRC cells by binding IGFIR inducing the PI3k-AKT/HKI axis leading towards abnormal glucose fermentation rates enhancing tumorigenicity within CRC cells[27]. EGF forms SRC/EGFR complexes while HGF forms c-Met receptor complexes both activating SRC enhancing aggressiveness

within CRC cells respectively Activated SRC up-regulates c-Met expression whereas EGF promotes interaction between HEG2 &CRC cell SRC[28] EGF-mediated SRC activation inhibits caspase 8 activity through FAS induced Tir380 phosphorylation thus hindering apoptosis within CRC cells In addition ERBB4 activation from SRC & EGFR led towards COXII upregulation hence enhancing CRC cell proliferation Activation of the EGF EGFR / SRC /NADPH oxidase signaling cascade leads towards NF-kB phosphorylation by AKT inducing NF-kB translocation. Activated NF-kB inhibits apoptosis with in CRC Cells by binding to HO-I gene promoter up regulating HO-I expression EGF-induced SRC activation enhances PEAK localization promoting cell proliferation migration tumor growth activating PXN, p130Cas ERK increase[29].

CONCLUSION

The treatment pathways of cultured bezoar in vitro for colorectal cancer mainly focus on cancer pathway, endocrine resistance, protean can in cancer, PI3K-Akt signaling pathway, tumor necrosis factor signaling pathway, etc., which is highly consistent with the treatment or chemotherapy of colorectal cancer. The clinical pharmacological effects of bezoar include immunity and anti-tumor effects, and its PI3K-Akt signaling pathway can promote cell growth and inhibit apoptosis, which is widely used in colorectal cancer. The application of bezoar is multi-purpose. This paper uses network pharmacology to explain the pharmacodynamic material basis of bezoar on colorectal cancer, and develop new ideas for its clinical treatment.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data and analysis, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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