Research on the Treatment of Colorectal Cancer Based on Network Pharmacology and Molecular Docking

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Abstract

Background: To predict the mechanism of Huaijiao Diyu Decoction in the treatment of colorectal cancer.

Methods: The active components and related targets of 7 kinds of Chinese medicinal materials were collected from the database of Chinese medicinal materials. CRC related targets are obtained from the Genes card database. cross targets of disease and drug targets were input into the STRING database to construct protein-protein interaction networks.GO enrichment analysis and KEGG enrichment analysis using clusterProfler packets in the language, Finally, the interaction between core components and core targets is discussed by molecular docking.

Result: TCMSP database prompts, There are 34 active compounds mapping 114 targets in Sophora japonica decoction; Genecards database prompts, A total of 858 targets are closely related to CRC, The two data sets map each other to obtain 114 intersection targets. Core components of Sophora flavescens decoction in treating CRC may be quercetin, kaempferol, luteolin, The core therapeutic targets may be PTGS2, PTGS1, HSP90AA1 and AR, CRC related pathways involve multiple molecular functions such as cell proliferation, apoptosis, cell signal transduction, metabolism, endocrine, tumor immunity, transcription and cell metabolism. Molecular docking results show that the binding ability of PTGS1, PTGS2, AR to core components is strong, The Vina value (binding energy) of the interaction between PTGS1 protein and core components is the best, -7.9kcal/mol.

Conclusion: This study demonstrates the mechanism of multi-component, multi-target and multi-pathway action in the treatment of CRC, Can provide the idea for clarifying the specific mechanism of Huaijiao Diyu decoction in the treatment of CRC in the future.

1. Background

Colorectal cancer is one of the most common malignancies in gastrointestinal tract[1], typical symptoms are hematochezia, abdominal pain, abdominal mass, weight loss, anemia, intestinal obstruction [2]. According to the latest report in 2018, globally, the incidence of colorectal cancer ranks fourth among malignant tumors, death rate ranked second [3]. January 2019, The National Cancer Center released the latest issue of national cancer statistics, the incidence and mortality of colorectal cancer in China ranked third and fifth respectively, The incidence of colorectal cancer in China is on the rise. The western medicine treatment of colorectal cancer is still mainly surgical treatment. And the only cure for colorectal cancer, Clinical use of surgery, radiotherapy, chemotherapy, targeted therapy and other treatment methods combined, fluorouracil (5 FU) based regiments and oxaliplatin were generally accepted as a standard adjuvant regimen [4]. But since most patients are diagnosed as advanced, Difficult treatment, Poor prognosis or long-term radiotherapy and chemotherapy lead to a serious decline in the quality of life of patients, Produce serious adverse reactions.

Traditional Chinese medicine is an important tumor-assisted treatment [5]. A number of studies have shown that Chinese medicine has played a positive role in blocking tumor energy metabolism, inducing
cancer cell apoptosis, reducing tumor cell recurrence and metastasis rate, and inhibiting tumor cell growth and value-added. Surgery, chemotherapy and taking Chinese herbal decoction were protective factors for CRC recurrence and metastasis has a positive effect on the survival time of CRC patients [6,7]. TCM believes that colorectal cancer has spleen and kidney yang deficiency, qi and blood deficiency, spleen deficiency dampness Sheng, spleen deficiency deficiency and other syndromes. Clinical practice has proved that Huaijiao Diyu decoction has a significant effect in the treatment of colorectal cancer, but its treatment mechanism is not clear and needs further exploration.

Sophora flavescens decoction from the "political criteria", for the main prescription for clearing heat and cooling blood, this prescription by Sophora flavescens, Radix Paeoniae Alba, Gardenia, Fructus Aurantii, Scutellariae, Schizonepeta. A result suggest that pretreatment with noncytotoxic concentrations of fructus sophorae extract (FSE) xhibits anti-inflammatory activity by inhibiting inflammatory media and cytokines through the inactivation of NF-κB, ERK and JNK, and it may offer therapeutic potential for creating inflammatory diseases associated with macroactivity [8]. The present results suggest that FSE may protect against inflammation and bone damage, and would be a valuable candidate for further investigation as a novel anti-arthritis agent [9].

Data suggested that the addition of SOWPa (from Sanguisorba officinalis L. Rosaceae) to PRP increased the reproductive capacity of ACL bers by blocking the TLR-4/NF-κB pathway. The addition of sowpa to prp can improve the regeneration ability of acl fibroblasts by blocking the tlr-4/nfb pathway. Components from Sanguisorba officinalis L. on Vibrio vulnificus have anti-bacterial effects and their soluble epoxide hydrolase inhibitory activity [11]. However, due to the characteristics of multi-component, multi-pathway and multi-target synergistic effect, this complexity makes the substance basis of traditional Chinese medicine is not clear, the mechanism of action is not clear, the quality of traditional Chinese medicine and traditional Chinese medicine is difficult to control, and the evaluation system of efficacy and safety is lacking. It is difficult to carry out comprehensive and systematic research from the whole to the level of tissues, organs, cells and molecules. Network pharmacology through the construction of "disease-gene-target-drug" interaction network, docking drugs and multiple disease targets and network analysis, systematic and comprehensive observation of drug intervention and impact on the disease network [12], It is helpful to reveal the material basis and mechanism [13] of traditional Chinese medicine or compound.

### 2. Materials And Methods

Chinese medicine believes that the pathogenesis of early colorectal cancer (colorectal cancer) is dampness and heat toxin accumulation of large intestine, qi and blood stasis is not smooth, its treatment principles should be to clear heat and dampness, blood stasis and detoxification, commonly used prescriptions such as Huaijiao Diyu decoction, Baeweng decoction, Xuefu Zhuyu decoction, etc. As shown in Fig.1.

#### 2.1 Collection of active compounds and targets
Through the TCMSP database (http://tcmspw.com/tcmsp.php), search for "Sophora japonica", "Ulmus pumila", "Fructus Aurantii", "Scutellaria baicalensis", "Schizonepeta", "Gardenia", "Radix Paeoniae Alba" seven herbs. Oral bioavailability (oral bioavailability) in pharmacokinetic (ADME) parameters was used in this study OB and drug-like properties (drug-likeness); and DL) as a standard, 30% OB ≥ set, DL ≥ 0.18 to screen active compounds and predict target [14] of active compounds in Sophora flavescens decoction. The Uniprot database (https://www.uniprot.org/) is used to standardize the target name.

2.2 Collection of CRC targets of active compounds in Sophora japonica L. Decoction

Through the Genecards database (https://www.genecards.org/) to "Colorectal cancer" as the keyword retrieval CRC action target [16]. The related targets of active compounds and CRC targets in Huaijiao Diyu decoction were mapped to obtain the intersection targets, and the R package VennDiagram was used to draw the Wayne map [17] of Huaijiao Diyu decoction and CRC related targets.

2.3 Traditional Chinese Medicine - Active Compounds - Construction of CRC- Target Network

The Chinese medicine, active compound, target and disease of Huaijiao Diyu decoction were introduced into the CRC Cytoscape 3.8.0 software to construct the "Chinese medicine-active compound- CRC- target" network. Analysis of topology parameters of network nodes using Network Analysis plug-ins, the core active compounds and core target [18] of Huaijiao Diyu decoction were screened by Degree value.

2.4 Building protein interaction networks

Using the string database (https://string-db.org/) to obtain target interaction [19], Homo sapiens", by selecting species Check "Hidden Network Interrupt Node hide disconnected nodes in the network", And set the "minimum required interaction score minimum required interaction score"≥0.9 to get the protein interaction network diagram and the core genes of the network, According to the number of connections with adjacent genes, the top 30 core genes histogram was obtained by R software. Import data cytoscape database to draw protein interaction network. Analysis of topology parameters of network nodes using Network Analysis plug-ins, According to the Degree value, the Sophora japonica decoction was screened.

2.5 Analysis of biological functions and pathways

ClusterProfiler is a software package for enrichment clustering and visualization of gene sets in R languages. Using the R language (version 4.0.3) to call the clusterProfiler package to analyze the GO molecular function and KEGG pathway enrichment of the target, Among them, the screening condition is that the P value is less than 0.05. The histogram and bubble chart [20] of GO function and KEGG path are drawn by using R package.

2.6 Molecular docking analysis of core active compounds with core protein receptors

The core active compounds of the first 4 and the core protein receptors of the first 4 were selected from the interaction network of the CRC targets treated Degree Huaijiao Diyu decoction. The structure of target
protein and core components are downloaded from PDB website (http://www.rcsb.org/) and pubchem website (https://pubchem.ncbi.nlm.nih.gov/) respectively. Using Pymol software to remove water and raw PDB, Autodock Tolls software for targeting protein receptor molecules with polar hydrogen, molecular docking through Autodock Vina and Python scripts. The lower the binding energy, the better the affinity between the receptor and the ligand. This study selected the binding energy $\leq -5.0 \text{ kJ/mol}$ as the screening basis for the effective binding of compounds and targets.

3. Results

3.1 Screening results of active compounds and targets in Sophora japonica

Enter the drug name in the TCMSP database, and according to $\text{OB} \geq 30$, $\text{DL} \geq$ the condition of 0.18, the active components of the drug were obtained. There were 13 active compounds of E. officinalis, six active compounds, Fructus Aurantii active compounds 5, There are 36 active compounds in Scutellaria baicalensis, There are 11 active compounds, Gardenia 5 active compounds, Radix Paeoniae Alba active compounds 13, A total of 64 active compounds were obtained after mapping, A total of 247 corresponding targets.

3.2 Results of intersection of active compounds in the treatment CRC action targets of Sophora japonica

The 858 CRC related potential targets were retrieved in the GeneCards database, and 114 intersection targets were obtained by mapping them with 247 targets corresponding to Huaijiao Diyu decoction, as shown in Fig.2.

3.3 Screening results of targets for the treatment of CRC by active compounds in Sophora flavescens decoction

To construct the network map of Chinese medicine - active compound - CRC - target by introducing CRC Chinese medicine, active compound, target and disease into the software, The network diagram consists of 172 nodes and 491 edges, Common goals and diseases containing 58 ingredients and 114 drugs. 114 common targets are considered as potential targets for the treatment of CRC by huaijiao diyu decoction (Fig.3). degree represents the total number of routes that other nodes in the network connect to that node. The higher the value, The more important the corresponding component or target is. After analysis using the circuit network analyzer plug-in in the Cytoscape software, Tables 1 and 2 list 10 major active components and 10 major targets, respectively. Table 1 shows, The highest degree component is PTGS2 (degree 48).

3.4 Building protein interaction networks

Use the string database (https://string-db.org/) to obtain target interaction relationships, Homo sapiens", by selecting species Check "Hidden Network Interrupt Node hide disconnected nodes in the network", And set the "minimum required interaction score minimum required interaction score" $>0.9$ to get the protein interaction network diagram and the core genes of the network (Fig.4), According to the number of
connections with adjacent genes, the top 30 core genes were obtained by R software (Fig.5). Import data cytoscape database to draw protein interaction network. Network Analysis plug-in analysis of the network diagram found, sorted by Degree values from high to low, AKT1, is the top 10 MAPK1, MAPK3, HSP90AA1, JUN, MAPK14, ESR1, CCND1, RB1, IL6 (Fig.6).

3.5 Analysis of biological functions and pathways

GO function analysis shows, 114 intersection targets predicted 145 enrichment results (pvalueCutoff <0.05, qvalueCutoff <0.05). DNA-binding transcription factor binding, included RNA polymerase II-specific DNA-binding transcription factor binding, ubiquitin-like protein ligase binding and transcription coactivator binding, Based on the results of screening the top 20 of the P values, See Fig.7, Fig.8.

KEGG enrichment analysis of Sophora flavescens decoction (p <0.05), The results show that 164 pathways were obtained, PI3K-Akt signaling pathway, MAPK signaling pathway and TNF signaling pathway were the representatives.. The top 20 pathways in KEGG enrichment analysis was demonstrated according to P value (Fig.9, Fig.10) Furthermore, they were mainly involved in antiviral, immunomodulatory and anti-inflammatory effects according to the function of these top 20 pathways (Table 3). Hepatitis B ID hsa05161) is the clearest pathway, see Fig.11.

3.6 Molecular docking

Molecular docking results show, There were 12 pairs of quercetin, luteolin, kaempferol, baicalin and other four core components < the Vina score of 5.0, indicating that the binding ability of PTGS1, PTGS2, AR and core components is strong, The Vina value (binding energy) of the interaction between PTGS1 protein and core components is the best, kcal/mol, -7.9 The specific docking results are shown in Table 4. Combined with Fig.12, quercetin form hydrogen bonds ARG376, GLN374 the amino acid residues of the PTGS2 protein, luteolin small molecules form hydrogen bonds THR206 the amino acid residues of the PTGS1 protein, wogonin small molecules form hydrogen bonds LYS93, TYR92 the amino acid residues of the AR protein.

4. Discussion

CRC is a common malignant tumor of digestive system, which can seriously affect the quality of life of patients. Huaijiao Diyu decoction has the function of reducing poison and increasing efficiency in the treatment of CRC, but its specific molecular mechanism and pharmacodynamic substance have not been fully elucidated. At present, network pharmacology and molecular docking technology have been applied to the screening of active compounds of traditional Chinese medicine and the docking of key targets on a large scale, which provides a possibility for the preliminary exploration of the action law of Huaijiao Diyu decoction in the treatment of CRC.

Analysis of active ingredients active ingredient analysis
Among the active ingredients, key ingredients with higher degree include quercetin, luteolin, kaempferol and wogonin. These four components belong to flavonoids, flavonoid phytoestrogens have been suggested to be associated with reduced risk of colorectal cancer [21]. A recent research showed that the combination of quercetin and exercise training exerts potent anti-tumour and anti-depressive effects through suppression of inflammation and upregulation of the BDNF/TrKβ/β-catenin axis in the prefrontal cortex in CRC treatment [22]. The combination of quercetin (Q) and alantolactone (A) is capable of reactive activity of immunity by education ICD, causing cell toxicity and modulating the immune-suppressive tumor microenvironment [23]. Jiamei Qi [24] found that alternating the consumption of β-glucan and quercetin alleviated colon damage and reduced the mortality rate in CRC mice. During colon cancer genesis, luteolin known to reduce oxidative stress thereby protects the cell to undergo damage in vivo. Wnt/β-catenin signaling, deregulated during neoplastic development, is modified by luteolin [25]. Thermosensitive in situ gel containing luteolin micelles has shown strong ability to promote tumor apoptosis, suppress tumor proliferation and block tumor angiogenesis [26]. Luteolin uppresses colorectal cancer cell metastasis via regulation of the miR 384/pleiotrophin axis [27]. Kaempferoll has a synergistic effect with 5FU by inhibiting cell proliferation and inducing apoptosis in colorectal cancer cells via suppression of TS or attenuation of p Akt activation. The combination of kaempferoll and 5FU may be used as an effective therapeutic strategy for colorectal cancer [28]. Reactive Oxygen Species and p53 Mediated Activation of p38 and Caspases is Critically Involved in Kaempferol Induced Apoptosis in Colorectal Cancer Cells [29]. Wogonin could inhibit the proliferation of SW480 cells through Wnt/β-catenin pathway [30]. Wogonin exerts growth inhibitory effects on the SW48 colorectal cancer cells by autophagic and apoptotic cell death, wogonin could also inhibit the PI3K/AKT and STAT3 signal transduction pathways [31]. Wogonin not only reduced tumor multiplicity, preserved colon length to normal but also didn't induce side effects on various organs [32].

Analysis of potential targets Potential Target Analysis

The target with the highest degree was PTGS2. The following targets were PTGS1, HSP90AA1, AR in the network of ingredient-target-disease. Prostaglandin endoperoxide synthase (PTGS), also known as cyclooxygenase (COX), which include inducible PTGS2 (cox-2) and constitutive PTGS1 (cox-1). HCT116 and HT29 could induce depolarization of granulocyte membrane potential after silencing by COX-1 gene, inhibiting adenosine triphosphate (ATP) production, increasing the content of reactive oxygen species, leading to apoptotic [33] in cancer cells. The association of tumour PTGS2 (COX-2) expression with colorectal cancer quality is strong in BRAF-mutated tumours than in BRAF-wild-type tumours [34]. Liu J and other [35] found Hsp90aa1 and dab2ip involved in the occurrence and metastasis mechanism of colorectal cancer. Heat shock protein 90 (HSP90) AA1 functions as an onco-protein to regulate the assembly, manipulation, folding and degradation of its client proteins, including c-MYC and Weidong Shi’s data revealed an unknown FBXL6-HSP90AA1-c-MYC axis which might contribute to the oncogenesis of HCC, and we propose that inhibition of FBXL6 might represent an effective therapeutic strategy for HCC treatment [36]. Repression of β2-AR but not β1-AR signaling selectively suppressed cell viability, induced G1-phase cell cycle arrest, caused both intrinsic and extrinsic pathways-mediated apoptosis of specific CRC cells and inhibited CRC-xenograft growth in vivo [37].
Analysis of PPI network

PPI network analysis

The target protein levels of AKT1, MAPK1, MAPK3, HSP90AA1 and JUN were excessively expressed in PPI network. This result indicated the series of targets of Huaijiao Diyu decoction treating CRC. AKT, also known as protein kinase B (PKB), is a downstream effector of the PI3K and is directly activated by it (PI3K Sator). Copanlisib promotes growth inhibition and apoptosis by modulating the AKT/FoxO3a/PUMA axis in colorectal cancer [38]. A novel coordination complex of platinum (PT) leads cell death in colony cancer by after reducing balance and modelling MAPK pathway [39]. ROS/JNK/c-Jun axis is involved in oridonin-induced caspase-dependent apoptosis in human colorectal cancer cells [40].

Analysis of signaling pathways Signal Pathway Analysis

The results of GO molecular functional clustering of 114 potential target genes in clusterProfiler package showed that the top 30 enrichment results involve many molecular functions, such as cell signal transduction, cell metabolism, transcription and redox, as well as antiviral, immunomodulatory and anti-inflammatory effects. KEGG pathway enrichment suggests, Possible CRC and PI3K-Akt signaling pathway, of Tongxie prescription MAPK signaling pathway and TNF signaling pathway closely related. Among them, Most CRC patients with abnormal PI3K/AKT signaling pathway and PI3K/Akt signal inhibitors are considered to be effective CRC therapeutic agents. PI3K/AKT signaling pathways can regulate the transcriptional expression of key miRNA, To enhance the [42] of resistance to proliferation and migration of CRC cells. Huijie Zhang and other [43] studies have found that regulating the activity of mapk signaling pathway can improve the depression behavior and survival state of the rat depression model. The RAS/MAPK axis regulates cancer cell proliferation, apoptosis, inflammation, migration, and metastasis [44]. Jobin and colleagues [45] found that targeting inflammation with TNF therapy has a preventative effect on carcinogenic activity of the microbiota in mouse models of colitis-associated colorectal cancer. Molecular docking indicates that the core components of Huaijiao Diyu decoction interact strongly with PTGS1·PTGS2·AR, suggesting that PTGS1·PTGS2·AR is probably an important target for the treatment of Huaijiao Diyu decoction.

Conclusion

This study used network pharmacology, molecular docking and other means to obtain 58 active compounds and 114 targets of CRC treated by Huaijiao Diyu decoction, and demonstrated the molecular relationship and the signal pathway covered by the GO function enrichment analysis, the KEGG pathway enrichment analysis, the construction of the CRC-target network and the key target verification. The results showed that there was a synergistic effect between traditional Chinese medicine, and showed that Huaijiao Diyu decoction could play a pharmacological role at the molecular level through multi-component, multi-target and multi-way, mainly involving many molecular functions such as cell signal transduction, cell metabolism, transcription and redox, as well as antiviral, immunomodulatory and anti-inflammatory effects. The overall understanding of the treatment CRC of Huaijiao Diyu decoction from an
intuitive point of view provides an important reference for the further study of the intervention CRC of Huaijiao Diyu decoction, which presents some advantages compared with the traditional pharmacological research. Limited by this study, only considering the quantitative relationship between traditional Chinese medicine, active compounds and targets, but not taking into account the effective intensity factors of active compounds and targets, the mechanism of action of drugs in vivo needs to be verified by further experiments. Therefore, more research methods should be carried out in the future to further reveal the mechanism of common prescriptions and their derived compounds in the treatment of colorectal cancer.

Abbreviation


Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

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Yujia Wang- WYJ
Jing Wu- WJ
Xingyu Chen- CXY
Ruitong Xu- XRT
Xingting Liu- LXT
Jingsong Luo- LJS
Tingting Deng- DTT

ZYW, DTT contributed to the conception of the study;
SXY performed the experiment;
SXY, WYJ contributed significantly to analysis and manuscript preparation;
ZYW, SXY, WJ performed the data analyses and wrote the manuscript;
CXY, XRT, LXT, LJS helped perform the analysis with constructive discussions.

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### Tables

**Table 1 Core targets of the top 10 in the network of Degree CRC- targets**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Degree</th>
<th>TopologicalCoefficient</th>
<th>NeighborhoodConnectivity</th>
<th>Radiality</th>
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<td>PTGS2</td>
<td>48</td>
<td>0.078683036</td>
<td>9.8125</td>
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<td>PTGS1</td>
<td>38</td>
<td>0.094976077</td>
<td>11.44736842</td>
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<td>HSP90AA1</td>
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<td>0.097054563</td>
<td>11.57894737</td>
<td>0.987772461</td>
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<td>AR</td>
<td>24</td>
<td>0.139823718</td>
<td>15.54166667</td>
<td>0.984886459</td>
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<td>PRSS1</td>
<td>23</td>
<td>0.142140468</td>
<td>15.7826087</td>
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<td>0.136363636</td>
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<td>0.971671603</td>
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<tr>
<td>CASP3</td>
<td>10</td>
<td>0.236792453</td>
<td>26.1</td>
<td>0.98306372</td>
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</tbody>
</table>
Table 2 Core Compounds with Top 10 Values in the Network of Degree CRC- Targets

<table>
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<th>Molecule Name</th>
<th>Degree</th>
<th>Source</th>
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<tr>
<td>MOL000098</td>
<td>quercetin</td>
<td>77</td>
<td>diyu, huaijiao, jingjie, zhizi</td>
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<td>MOL000006</td>
<td>luteolin</td>
<td>40</td>
<td>jingjie</td>
</tr>
<tr>
<td>MOL000422</td>
<td>kaempferol</td>
<td>28</td>
<td>baishao, diyu, huaijiao, zhizi</td>
</tr>
<tr>
<td>MOL000173</td>
<td>wogonin</td>
<td>27</td>
<td>huangqin</td>
</tr>
<tr>
<td>MOL002714</td>
<td>baicalein</td>
<td>23</td>
<td>huaijiao, huangqin</td>
</tr>
<tr>
<td>MOL005828</td>
<td>nobiletin</td>
<td>21</td>
<td>zhike</td>
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<td>5,7,4'-Trihydroxy-8-methoxyflavone</td>
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<td>huangqin</td>
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Table 3 Information of potential targets and signaling pathways
<table>
<thead>
<tr>
<th>ID</th>
<th>Description</th>
<th>pvalue</th>
<th>Count</th>
</tr>
</thead>
<tbody>
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<td>hsa04151</td>
<td>PI3K-Akt signaling pathway</td>
<td>3.73E-20</td>
<td>34</td>
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<tr>
<td>hsa05161</td>
<td>Hepatitis B</td>
<td>2.23E-30</td>
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<td>hsa05167</td>
<td>Kaposi sarcoma-associated herpesvirus infection</td>
<td>3.71E-25</td>
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<td>hsa05163</td>
<td>Human cytomegalovirus infection</td>
<td>9.96E-21</td>
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<td>hsa05166</td>
<td>Human T-cell leukemia virus 1 infection</td>
<td>6.46E-20</td>
<td>28</td>
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<td>hsa05215</td>
<td>Prostate cancer</td>
<td>8.43E-29</td>
<td>27</td>
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<td>hsa05169</td>
<td>Epstein-Barr virus infection</td>
<td>1.01E-19</td>
<td>27</td>
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<td>hsa04210</td>
<td>Apoptosis</td>
<td>3.99E-23</td>
<td>26</td>
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<tr>
<td>hsa05205</td>
<td>Proteoglycans in cancer</td>
<td>2.05E-18</td>
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<td>hsa05206</td>
<td>MicroRNAs in cancer</td>
<td>5.60E-14</td>
<td>26</td>
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<td>hsa05165</td>
<td>Human papillomavirus infection</td>
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<td>hsa01522</td>
<td>Endocrine resistance</td>
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<td>hsa05170</td>
<td>Human immunodeficiency virus 1 infection</td>
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<td>hsa04010</td>
<td>MAPK signaling pathway</td>
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<td>hsa05022</td>
<td>Pathways of neurodegeneration -multiple diseases</td>
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<td>hsa04218</td>
<td>Cellular senescence</td>
<td>7.86E-18</td>
<td>23</td>
</tr>
<tr>
<td>hsa05225</td>
<td>Hepatocellular carcinoma</td>
<td>4.31E-17</td>
<td>23</td>
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</table>

Table 4 Binding energies of key active compounds with core targets

<table>
<thead>
<tr>
<th>Mol ID</th>
<th>Molecule Name</th>
<th>PTGS1</th>
<th>PTGS2</th>
<th>HSP90AA1</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOL000098</td>
<td>quercetin</td>
<td>-5.4</td>
<td>-7.9</td>
<td>-4.2</td>
<td>-7.5</td>
</tr>
<tr>
<td>MOL00006</td>
<td>luteolin</td>
<td>-6.3</td>
<td>-7.9</td>
<td>-4.2</td>
<td>-7.3</td>
</tr>
<tr>
<td>MOL000422</td>
<td>kaempferol</td>
<td>-5.4</td>
<td>-7.9</td>
<td>-4.2</td>
<td>-7.1</td>
</tr>
<tr>
<td>MOL000173</td>
<td>wogonin</td>
<td>-6.2</td>
<td>-7.9</td>
<td>-4.2</td>
<td>-7.5</td>
</tr>
</tbody>
</table>

Figures
Figure 1

- Active compounds
- Target
- Colorectal cancer
- Disease targets
- Network and pathway analysis
- Molecular docking

Venn diagram:

- Disease: 744
- Drug: 114
- Overlap: 133
Figure 2

Venn diagram of Huaijiao Diyu decoction-CRC related targets (the large circle on the left represents the CRC related potential target, the small circle on the right represents the related potential target of Huaijiao Diyu decoction, and the middle represents the intersection target.)

Figure 3
The network of diagram of herbs-active compounds-targets (triangle represents CRC, rectangle represents the corresponding active compounds of traditional Chinese medicine, oval represents the target of active compounds, light pink represents Scutellaria baicalensis and its corresponding active compounds, light blue indicates Schizonepeta mutiDrug, gray indicates Schizonepeta and its corresponding active compounds, dark yellow indicates Ulmus pumila and its corresponding active compounds, orange indicates Sophora japonica and its corresponding active compounds, red indicates Fructus Aurantii and its corresponding active compounds, light green indicates gardenia and its corresponding active compounds. )
Figure 4

The network of protein to protein interaction (PPI)
Figure 5

The top 30 core genes
Figure 6

The core target of Degree top 10 in the network of protein interactions (AKT1, MAPK1, MAPK3, HSP90AA1, JUN, MAPK14, ESR1, CCND1, RB1, IL6)

[Diagram showing protein interactions and node rank table]
Figure 7
GO function histogram of the key targets of Huaijiao Diyu decoction in treatment of CRC

Figure 8
GO pathway enrichment bubble chart of the key targets of Huaijiao Diyu decoction in treatment of CRC
Figure 9

KEGG function histogram of the key targets of Huaijiao Diyu decoction in treatment of CRC
Figure 10

KEGG pathway enrichment bubble chart of the key targets of Huaijiao Diyu decoction in treatment of CRC
Figure 11

Distribution of target protein in the prediction pathway of Sophora japonica
Figure 12

The molecular docking diagram of quercetin and PTGS2, Luteolin and PTGS1, Kaempfero and HSP90AA1, Wogonin and AR

Supplementary Files

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• Supplementaryinformation.docx