

Traditional Chinese Medicine in Colorectal Cancer Therapy: A Focus on *Panax quinquefolium* L. through Text Mining and Network Medicine Approaches

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Abstract

Background: This study aimed to identify traditional Chinese medicines (TCMs) with potential anti-colorectal cancer (CRC) properties and their core active constituents. **Methods:** A comprehensive review of the literature regarding CRC treatment using TCM was conducted using the PubMed database. A text mining approach was employed to ascertain the correlation between TCM and CRC, highlighting the top ten TCMs. The most significantly correlated TCM underwent network medical analysis. Component data were sourced from the TCMSP and HERB databases, while their targets were identified through public databases. Concurrently, various databases were utilized to pinpoint CRC-associated target genes. Network medicine was then employed to ascertain the network proximity between component targets and CRC genes. Potential targets for both TCMs and CRC were mapped and were subsequently input into the String database to craft a protein-protein interaction (PPI) diagram. Visualization and analysis of the TCM-ingredients-targets and PPI diagrams were performed using Gephi 0.9.2. Lastly, DAVID database was used for GO and KEGG pathway enrichment analyses of the intersecting targets. **Results:** Text mining revealed *Panax quinquefolium* L. displays the most pronounced anti-CRC properties. Notably, key ingredients of *Panax quinquefolium* L., including Ginsenoside Rb3, Papaverine, Ginsenoside Rg3, and Ginsenoside Rb1, were found to have substantial impacts on cancer and microRNA-cancer signaling pathways. **Conclusions:** The TCM *Panax quinquefolium* L. showcases a strong potential in CRC treatment, particularly due to the efficacy of Ginsenoside Rb3 and Ginsenoside Rg3. This study provides a foundational analysis for further exploration into the therapeutic effects and underlying mechanisms of *Panax quinquefolium* L. in combating CRC.



1 Introduction

Cancer is a problem for public health worldwide. According to statistics, there were 1,670 cancer-related fatalities and 5,370 new cases of cancer identified in America in 2023. Nevertheless, over the previous ten years, the death rate from CRC has declined annually by 2% [1]. CRC is a malignant tumor occurring from the cecum to the rectum, including rectal cancer and colon cancer, which is one of the three most common cancers globally. According to the 2020 global cancer statistics, CRC had the third highest incidence [2] and was the second leading cause of death for women [3,4]. The main causes of CRC are long-term inflammatory bowel illness, personal and family medical histories, prolonged inactivity, poor diet, and alcohol consumption [5]. Nowadays, surgical resection combined with chemotherapy is the mainstay of CRC treatment. However, the 5-year survival rate is low, and chemotherapy has significant hazardous side effects [6]. Hence, new treatment schemes and strategies are of great significance, and notably, TCM combined with chemotherapy has unique advantages in the prognosis of CRC patients [7,8].

TCM offers a broad range of opportunities for disease prevention and therapy with its emphasis on holism and extensive treatment history with various ingredients [9]. Many studies have been conducted on anti-CRC properties of TCM and how important they are for treating and preventing CRC. TCM was reported that it inhibits angiogenesis and CRC cell proliferation, boosts immunity, and prolongs CRC patient lifespan [10]. The capacity of TCM to regulate a variety of signaling pathways, such as Phosphatidylinositol 3-kinase/protein kinase-B (PI3K/Akt) signaling pathway, Nuclear factor kappa-beta (NF- κ B) signaling pathway, Mitogen-activated protein kinase (MAPK) signaling pathway, and immunomodulatory signaling pathways.

Such regulation impacts key biological processes like cell proliferation, apoptosis, cell cycle progression, and chemoresistance, thereby exerting a multifaceted therapeutic influence on CRC [10]. Due to the complex mechanism of TCM in CRC patients, its active ingredients and action mechanisms need systematic exploration. In recent years, with the combination of new technologies and TCM research, achievements have been made in research on the modernization of TCM. Network medicine is an emerging discipline based on computer technology, systems biology network analysis, and multi-target drug molecular design [11], which features “holism” and “systematization” [12,13]. This technology provides new possibilities for unveiling the multiple mechanisms of TCM in treating CRC.

This study (Figure 1) summarized the literature about anti-CRC TCM in the PubMed database and identified the potential TCM that can effectively treat CRC. Later, the active ingredients and mode of action of TCM in the treatment of CRC were identified by network medical analysis, offering a theoretical foundation and empirical support for the use of TCM in the treatment of CRC.

2 Methods

2.1 Collection of anti-CRC TCM

To obtain effective anti-CRC TCM, literature about the treatment of CRC with TCM was collected through text analysis on the PubMed database. A total of 14,558 pieces of literature on CRC were retrieved with “Colorectal cancer”, “Colorectal neoplasms”, “Colorectal tumors”, “Colorectal carcinoma” and “Colorectal” as keywords, and by limiting keywords in the title/abstract. Regarding the previously published report, “Herbal medicine” and “Colorectal cancer” were used as keywords [14], and 83 TCMs that were reported to be applied to treat CRC were retrieved (Data deadline: September 2023). Next, the correlation between TCM and CRC was measured

according to a reported formula [15], using R language software version 4.3.0 to rank the correlation of TCM. The formula was as follows, where N represents the total number of articles on the PubMed database, n represents the number of articles involving a single TCM, K represents the total number

of articles involving CRC, and k represents the number of articles involving a single TCM related to CRC.

$$P = 1 - \sum_{i=0}^{k-1} f(i) = 1 - \sum_{i=0}^{k-1} \frac{\binom{K}{i} \binom{N-K}{n-i}}{\binom{N}{n}}$$

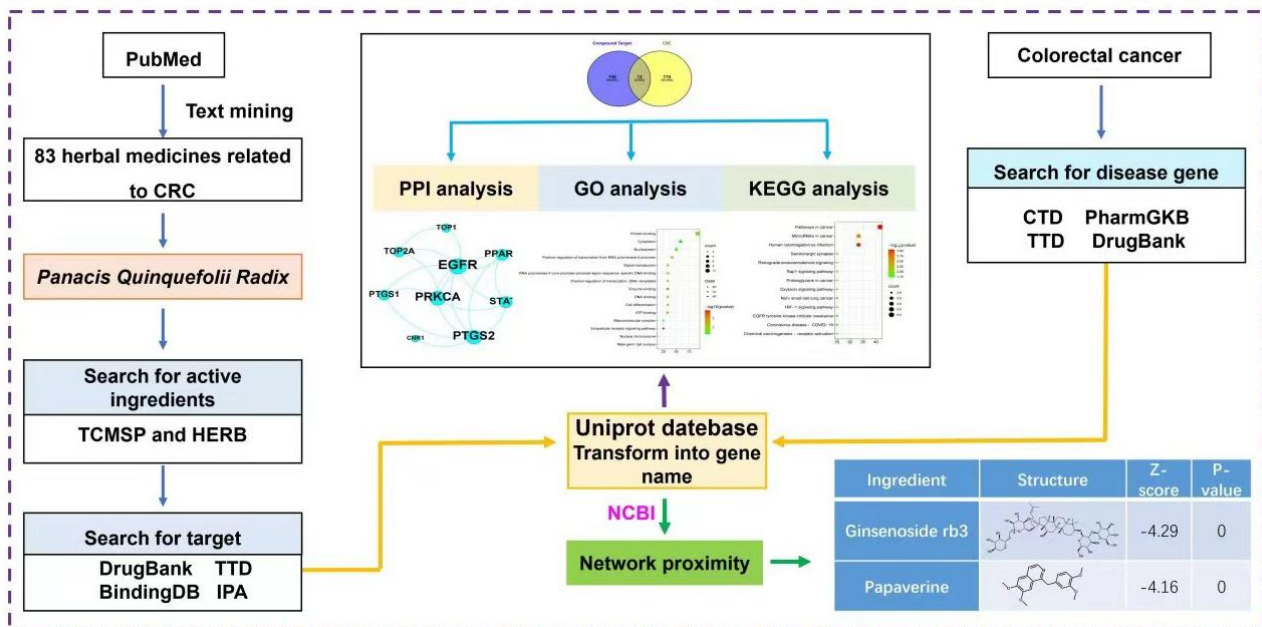


Figure 1 Detail chart of this study.

2.2 Screening of active ingredients in TCM

The ingredients of TCM were acquired using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <https://www.tcmsp-e.com/>) and HERB databases (a high-throughput experiment- and reference-guided database of traditional Chinese medicine, <http://herb.ac.cn>) [16,17]. Of them, TCMSP combined with kinetic parameters was applied to set oral bioavailability (OB) ≥ 30 and drug-likeness (DL) ≥ 0.18 , to screen out qualified TCM ingredients. Then, these ingredients were summarized, duplicates were removed, and the data was saved in Excel for subsequent data processing.

2.3 Screening of targets active ingredients of indicated TCM

In this paper, the collected ingredients were analyzed

on DrugBank (<https://go.drugbank.com/>), TTD (<http://db.idrblab.net/ttd/>), BindingDB (<https://www.bindingdb.org/bind/index.jsp>), and IPA software to obtain relevant component targets. The ingredient targets from each database were summarized to remove duplicates and were converted into gene names using the UniProt database (<https://www.uniprot.org/>). The species was limited to "Homo sapiens". The obtained gene names were converted into Gene ID via NCBI database (<https://www.ncbi.nlm.nih.gov/>) for further calculation of network proximity. Detailed ingredients and target information are shown in [Supplementary Material 1](#).

2.4 Collection of CRC genes

Using "Colorectal cancer" as the keyword, genes associated with CRC were retrieved through 4 databases CTD (<http://ctdbase.org>), TTD, DrugBank,

and PharmGKB (<http://www.pharmgkb.org>). The ingredient targets and CRC-related genes were imported into the online tool Venny 2.1.0 (<http://bioinformatics.psb.ugent.be/>), and the intersection part was the potential target of TCM in treating CRC. Detailed disease genes were shown in [Supplementary Material 2](#).

2.5 Calculation of network proximity

Network proximity is the shortest distance (dc) between drug targets (T) and disease-related genes (S). In line with a former study, the dc between T and S in the human interaction group was calculated, and then a reference distribution distance was established to evaluate the importance of drugs and diseases. T and S with the same network distance were calculated 1000 times to obtain the Z-Score [18]. The online calculation website is <http://www.zmupredict.cn/proximity>. When the Z-Score < -1.5 and $p \leq 0.05$, the TCM ingredients were considered to have a pharmacologic action. For more details, please refer to our previous research [19,20].

2.6 Protein-protein interaction (PPI) network diagram

The intersecting targets of TCM ingredients and CRC were collected through Venny 2.1.0, and the potential targets were imported into String database (<https://www.string-db.org/>), with the species limited to "Homo Sapiens". Edge and node data were saved and imported into Gephi 0.9.2 software to plot PPI network diagram.

2.7 Plotting of TCM-ingredients-targets diagram

The data were imported into Gephi 0.9.2 software to create a visualized TCM-ingredients-targets diagram.

2.8 GO enrichment and KEGG pathway analyses of anti-CRC TCMs

To acquire GO enrichment and KEGG pathway

analyses of TCM ingredients targets and disease-related genes, the intersecting targets of TCM and disease were imported into DAVID database (<https://david.ncifcrf.gov/>), with the species limited to "Homo Sapiens". Then, the main pathways and annotated genes were singled out, and microbioinformatics (a plotting website) was employed to conduct visualized analyses. GO enrichment covers three types, namely molecular function (MF), biological process (BP), and cellular component (CC).

3 Results and analyses

3.1 The top ten TCMs highly correlated with CRC

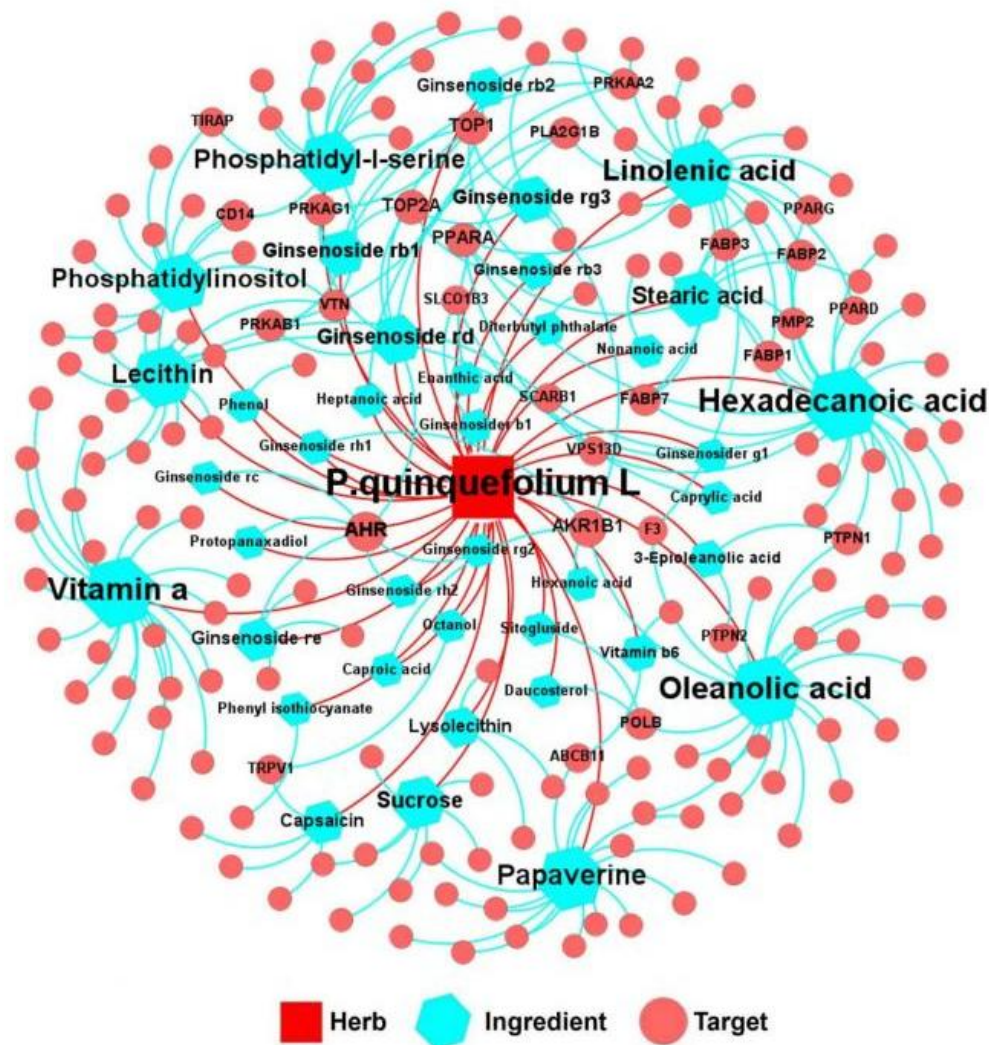
Through literature collection, correlation calculation, and ranking, the top ten TCMs highly correlated with CRC were identified, including *Panax quinquefolium* L., *Scutellaria barbata* D.Don, *Panax Ginseng* C. A. Mey., *Salvia miltiorrhiza* Bge., *Ganoderma lucidum*, *Zingiber officinale* Rosc., *Salvia japonica* Thunb., *Glycyrrhiza uralensis* Fisch, *Sophora flavescens* Ait and *Paris polyphylla* Smith var. *chinensis* (Franch.) Hara ([Table 1](#)). Among them, *Panax quinquefolium* L. ranked first, accounting for 38.60% ($p = 7.51\text{E-}60$) and *Scutellaria barbata* D.Don ranked second, accounting for 11.31% ($p = 1.70\text{E-}40$). $p \leq 0.01$ represents a high correlation. Therefore, these TCMs had a remarkable anti-CRC effect.

3.2 *Panax quinquefolium* L.-target network diagram

TCM features multi-ingredients and multi-targets, which commonly perform extensive pharmacologic actions through multiple ingredients and targets. *Panax quinquefolium* L. having the highest correlation with CRC, was selected for subsequent network visualized analyses. According to [Figure 2](#), there were 202 nodes and 255 edges. A greater number of ingredient targets mean a higher degree. [Figure 2](#) only displayed labels with nodes of degree ≥ 2 .

Table 1 The top ten TCMs highly correlated with CRC treatment.

| Latin name | Chinese name | Total | Relevant to CRC | Rate (%) | p-value |
|---|--------------|-------|-----------------|----------|----------|
| <i>Panax quinquefolium L.</i> | Xiyangshen | 57 | 22 | 38.60 | 7.51E-60 |
| <i>Scutellaria barbata D.Don</i> | Banzhilian | 168 | 19 | 11.31 | 1.70E-40 |
| <i>Panax Ginseng C. A. Mey.</i> | Renshen | 5425 | 31 | 0.57 | 4.58E-25 |
| <i>Salvia miltiorrhiza Bge.</i> | Danshen | 136 | 12 | 8.82 | 9.14E-25 |
| <i>Ganoderma lucidum</i> | Lingzhi | 2461 | 23 | 0.93 | 1.14E-23 |
| <i>Zingiber officinale Rosc.</i> | Shengjiang | 751 | 14 | 1.86 | 4.23E-19 |
| <i>Salvia japonica Thunb</i> | Gouweicao | 172 | 10 | 5.81 | 5.20E-19 |
| <i>Glycyrrhiza uralensis Fisch</i> | Gancao | 1102 | 13 | 1.18 | 2.61E-15 |
| <i>Sophora flavescens Ait</i> | Kushen | 312 | 9 | 2.88 | 1.75E-14 |
| <i>Paris polyphylla Smith</i> var. <i>chinensis</i> (Franch.) Hara | Chonglou | 270 | 8 | 2.96 | 4.04E-13 |

**Figure 2** TCM-ingredients-targets network diagram. (Red: *Panax quinquefolium L.*; Blue: TCM ingredients; Pink: TCM targets.)

3.3 Calculation results regarding the network proximity of TCM-targets and CRC-related genes

Concerning an existing report, we calculated the shortest distance between TCM ingredient targets and CRC-related genes in the human interaction group to evaluate the therapeutic efficacy of active ingredients on CRC. The ingredients and targets of *Panax quinquefolium L.* were collected from a public database. There were 39 ingredients with 162 targets, and 186 CRC-related genes. The results were exhibited in Table 2. The ranking was completed based on Z-Score. A lower Z-Score signifies a closer distance and a high correlation. Our results indicated that Z-Scores of Ginsenoside Rb3, Papaverine, Ginsenoside Rg3, and Ginsenoside Rb1 were all below -1.5, which may be the key ingredients of *Panax quinquefolium L.* for anti-CRC. Detailed results of the network proximity calculations were presented in Supplementary Material 3.

3.4 Venn diagram of “TCM-disease” targets and PPI analyses

Biological functions or pathways may play roles in the regulation of relevant proteins. We adopted PPI to elucidate the effective ingredients and mechanism of *Panax quinquefolium L.* for anti-CRC. 12 intersecting targets were obtained after the retrieved 162 ingredient targets and 186 CRC-related genes were made into Venn diagram (Figure 3). Then, the intersecting targets were imported into String database to obtain the interaction diagram of potential targets. The results revealed that epidermal growth factor receptor (EGFR) (degree = 7), protein kinase C alpha (PRKCA) (degree = 6), and prostaglandin-endoperoxide synthase 2 (PTGS2) (degree = 6) had relatively high degrees, which may be the critical genes to treat CRC.

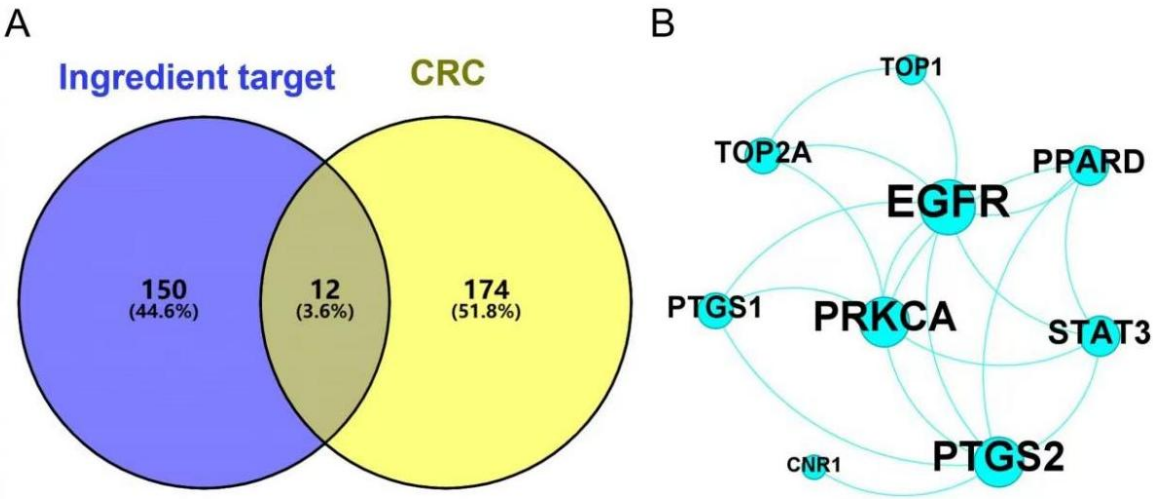
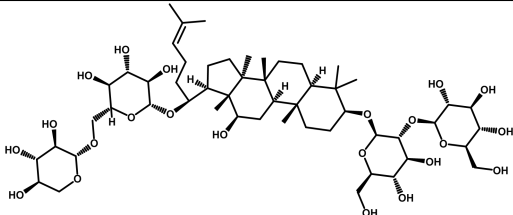
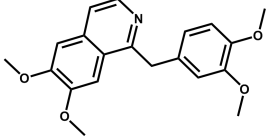
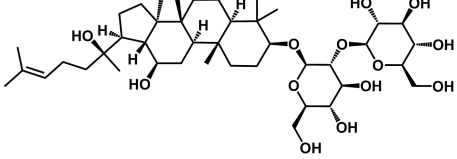
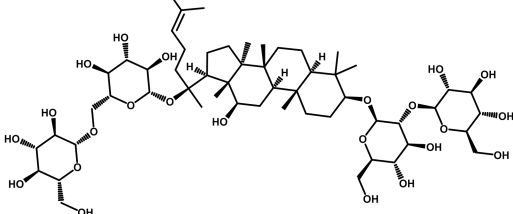
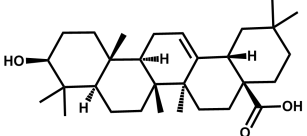
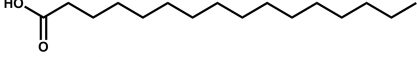
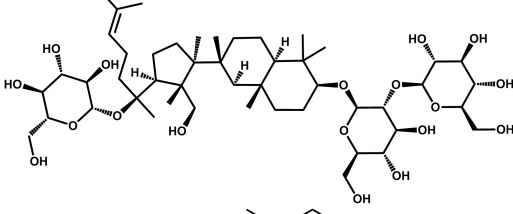
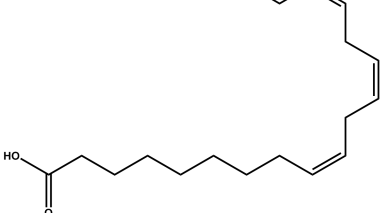
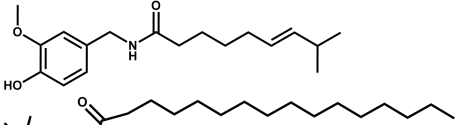
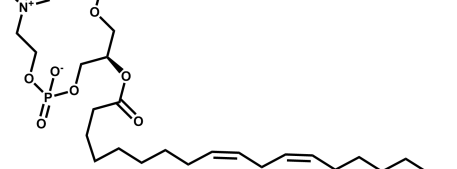


Figure 3 Venn diagram of *Panax quinquefolium L.* against CRC and PPI analyses. (A) Intersecting targets of component targets and CRC-related genes; (B) PPI network diagram.

Table 2 The predicted top ten active components of *Panax quinquefolium* L. based on network proximity.

| Ingredient | Chemical structure | Z-score | p-value | Related literature |
|-------------------|---|---------|---------|----------------------|
| Ginsenoside rb3 |  | -4.29 | <0.001 | [19] |
| Papaverine |  | -4.16 | <0.001 | - |
| Ginsenoside rg3 |  | -4.12 | <0.001 | [20] |
| Ginsenoside rb1 |  | -3.38 | <0.001 | [21] |
| Oleanolic acid |  | -3.35 | <0.001 | [22] |
| Hexadecanoic acid |  | -3.31 | 0.003 | [23] |
| Ginsenoside rd |  | -3.15 | <0.001 | [24] |
| Linolenic acid |  | -3.08 | 0.004 | [25] |
| Capsaicin |  | -3.01 | 0.001 | [26] |
| Lecithin |  | -1.95 | 0.019 | - |

“-” means no directly relevant reports.

3.5 GO enrichment and KEGG pathway analysis results

To thoroughly explore the biological function of *Panax quinquefolium L.* in treating CRC, we used DAVID online database to conduct GO functional enrichment and KEGG pathway analyses, and created GO and KEGG bubble diagrams using microbioinformatics online plotting website. The top five BP, CC, and MF were subjected to GO enrichment analyses based on Count value (Figure 4). These functions predominantly

encompass the positive regulation of transcription from RNA polymerase II promoter, cytoplasm, and protein binding. Furthermore, we selected the top ten pathways for KEGG pathway analysis based on their count values. The resulting bubble diagram, presented in Figure 5, highlights the gene enrichment pathways relevant to CRC treatment. These pathways predominantly involve mechanisms in cancer, microRNAs (miRNAs) in cancer, human cytomegalovirus infection, and the Rap1 signaling pathway.

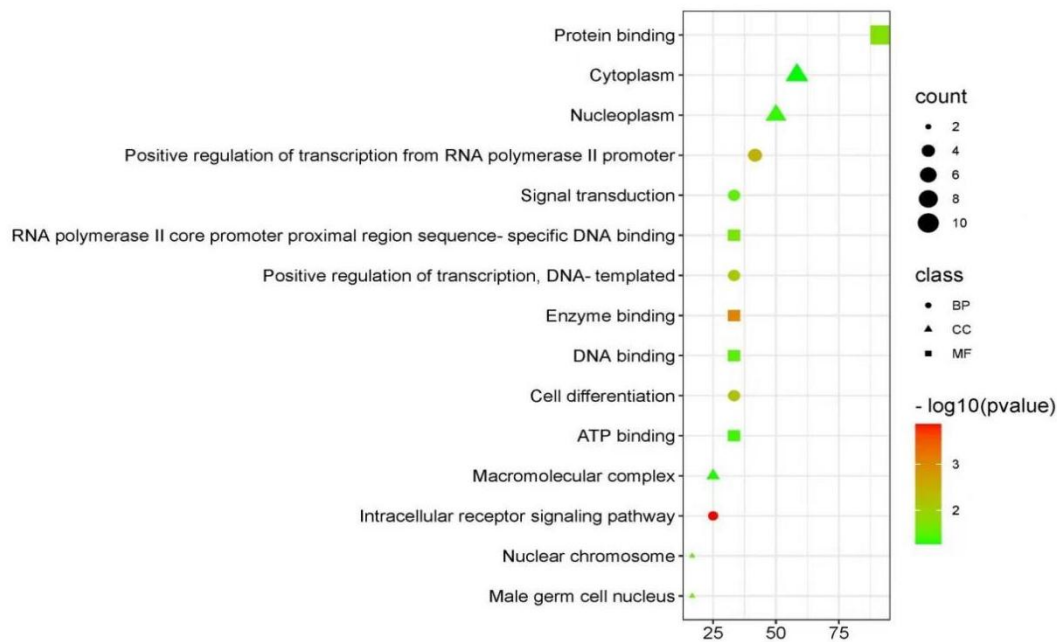


Figure 4 GO enrichment analysis of potential targets. (Circle: BP; Triangle: CC; Quadrate: MF.)

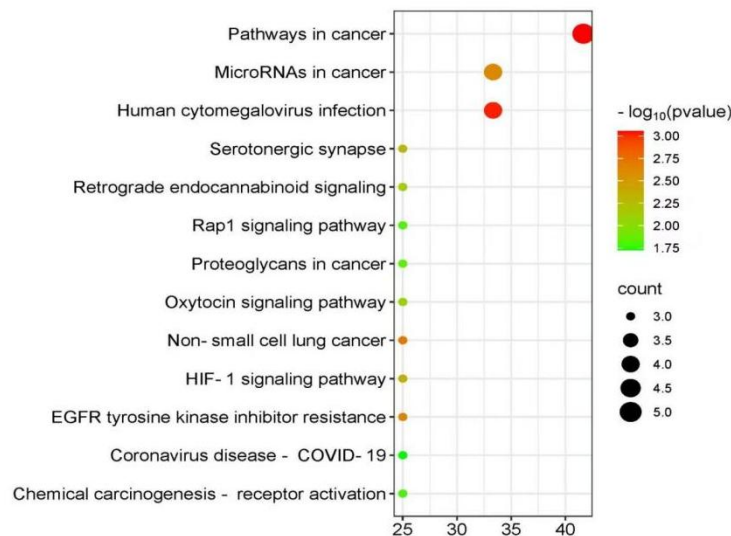


Figure 5 Bubble diagram of KEGG pathway analysis. Larger bubble and darker color imply stronger correlation of the pathway.

4 Conclusion and perspective

This study examined the active ingredients and mechanisms based on the top-ranked TCM, as well as the promising anti-CRC TCMs, using text mining and network medicine. Ten TCMs, including *Panax quinquefolium* L., *Scutellaria barbata* D.Don, *Panax ginseng* C. A. Mey, showed a strong connection with CRC, according to text mining results. *Panax quinquefolium* L. can tonify qi, nourish yin, clear heat, and produce fluid; *Scutellaria barbata* D.Don can clear heat, remove toxins, resolve stasis, and promote urination; and *Panax Ginseng* C. A. Mey can tonify the spleen and replenish the lung, according to the efficacy of TCMs documented in the Chinese Pharmacopoeia (2020 edition). TCM emphasizes "treatment with both elimination and reinforcement" in accordance with the principle of "treatment based on syndrome differentiation". In addition to suppressing cancer cell growth, TCM also improves physical health and immunity to help intestinal cancer patients recover better and faster. The subsequent analyses were performed on TCM which had the highest correlation with CRC. The results of network proximity showed that Ginsenoside Rb3, Papaverine, Ginsenoside Rg3, and Ginsenoside Rb1 may be the key active ingredients to treat CRC, and EGFR, PRKCA, and PTGS2 were potential targets. KEGG pathway analysis data indicated that pathways in cancer are pivotal anti-CRC pathways. These findings theoretically guide the follow-up clinical medication and provide novel research thoughts to expound on the active ingredients and mechanisms of TCM in treating CRC.

In previous reports, *Panax quinquefolium* L. and its extract have been widely applied to treat cardiovascular diseases [27], diabetes, and chronic obstructive pulmonary disease [28,29]. The main ingredients of *Panax quinquefolium* L. are Ginsenosides (Rb1, Rb2, Rg3, Re, and Rd), and consistent with previous reports, we found that

Ginsenoside Rb3, Ginsenoside Rg3, Ginsenoside Rb1, and Ginsenoside Rd were ranked in the top ten of active ingredients in *Panax quinquefolium* L.. Ginsenoside Rg3 can be used to treat various CRC cells, which has a strong therapeutic effect through mediating protein expressions of C/EBP β /NF- κ B pathway to dampen CRC cell proliferation [21,22]. Relative to other saponins, Ginsenoside Rb3 has a weak effect on anti-CRC, 300 μ M of which barely affecting CRC cell proliferation [21]; however, by anti-inflammation and anti-oxidant stress effects, Ginsenoside Rb3 can impact other diseases, such as exerting protective properties against cigarette smoke extract-induced cell injury and fibrosis [30]. Moreover, Ginsenoside Rb3 has been confirmed to play an anti-cancer role by restoring mucosal structure, improving mucosal immunity, promoting probiotic growth, and reducing relevant flora [31]. It has been documented that Ginsenoside Rb1 can inhibit the proliferation of SW480 cells [32], which similarly decreases myocardial infarction area while attenuating fibrosis and reperfusion injury through inhibiting reactive oxygen species production from mitochondrial complex I [33]. Ginsenoside Rd has been verified to inhibit CRC cell migration via EGFR [26]. Furthermore, in the calculation of our top ten ingredients, fatty acids were also included, such as linolenic acid, hexadecanoic acid, and oleanolic acid. Reportedly, these ingredients can suppress tumor cell growth based on different mechanisms. Linolenic acid plays an anti-cancer role through declining oxidative phosphorylation and glycolysis to render the tumor cells in a resting state [27]. Oleanolic acid is capable of dampening the proliferation of tumors *in vivo* and *in vitro* [24]. Hexadecanoic acid can treat cancer by blocking epithelial-mesenchymal transition in CRC cells and reducing tumor-related macrophages [25]. Besides, papaverine occupied the second position in active ingredients, with multiple pharmacologic actions, such as anti-cancer, anti-inflammation, and

neuroprotection. The papaverine derivative caroverine inhibits the expression of VEGF in CRC cells to attenuate the toxic effect of linoleic acid hydroperoxide on cells [32]. Pepper is composed of about 69% capsaicin which has anti-inflammation and anti-oxidant properties, and can treat CRC by mediating cell cycle arrest, proliferation, and apoptosis [28]. Lecithin is mainly derived from plant species, including soybeans, sunflowers, and canola seed, which has functions in micelles and oil-in-water emulsions and can improve the rate of drug release and administration mode [34,35], but little is reported about its therapeutic effect on cancer. Collectively, the first nine of the top ten ingredients have anti-cancer effects, and thus this method has certain advantages in predicting drugs.

EGFR is a kind of transmembrane protein, belonging to the Erythroblastic Leukemia Viral Oncogene Homolog (ERBB) family, the expression level of which in CRC patients has an intimate association with tumor cell proliferation. In *in-vitro* CRC cell models, knocking down EGFR expression can inhibit CRC cell proliferation and migration [36]. Therefore, EGFR has been extensively considered to be the promising target of CRC treatment. Additionally, PRKCA suppresses WNT activity to increase the survival rate of CRC patients [37]. PTGS2 is not expressed on normal rectal mucosa, but the deficiency of PTGS2 is more likely to cause neutrophil infiltration or slow ulcer healing, ultimately inducing CRC [38]. There is a study unveiling that PTGS2 is remarkably overexpressed in tumor tissues [39]. In our prediction results, EGFR, PRKCA, and PTGS2 had high degrees, which may be the critical genes to treat CRC.

Next, we analyzed KEGG pathways and GO enrichment for 12 targets. The three primary components of GO enrichment analysis are protein binding, cytoplasm, and positive regulation of transcription from the RNA polymerase II promoter.

EGFR tyrosine kinase inhibitor resistance, Rap1 signaling routes, HIF-1 signaling pathways, cancer-related mRNA pathways, and other pathways are the main pathways in KEGG pathway analysis. Various tumor cells ability to proliferate, migrate, and remain viable can be inhibited by miRNA; in fact, people with CRC have much higher levels of miRNA in their plasma. MiRNA may therefore be used as a prospective biomarker for CRC screening and treatment planning [40,41]. According to a former report, Mex3a is remarkably high expressed in tumor tissues and mediates CRC cell proliferation and migration via the Rap1 signaling pathway [42]. Tumor development and metastasis may be inhibited by HIF-1 downregulation [43]. EGFR is the key factor for cell proliferation and differentiation, and despite its prominent role in CRC chemotherapy, the effect of EGFR monoclonal antibody is often limited by drug resistance [44]. It has been shown that tyrosine kinase inhibitors can reduce the resistance of anti-EGFR treatments in colorectal cancer [45]. These pathways have a close relationship with CRC and provide references for subsequent research on the pathogenesis of CRC.

This research utilizes text mining and advanced network medical computing to identify potential anti-colorectal cancer (CRC) Traditional Chinese Medicines (TCMs). It further conducts in-depth network medical computing and visual analysis, focusing specifically on the TCM exhibiting the highest correlation with CRC. A notable limitation of this study is the lack of extensive *in vitro* or *in vivo* experimental validation. Consequently, further elucidation of the underlying mechanisms is warranted. TCM, known for its low toxicity, fewer side effects, and multi-ingredient, multi-target characteristics, presents a compelling area of study. Employing network medicine techniques, this study determines the network proximity between active TCM ingredients and illness-related genes, where a lower Z-score signifies greater relevance. This

approach offers a valuable framework for assessing the potential therapeutic efficacy of TCM monomers. Ultimately, this research comprehensively delineates the active ingredients, targets, and effective pathways of TCM, thereby contributing significantly to the clinical application and experimental investigation of anti-CRC TCMs.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: A.R. and M.L.; Data curation: M.H. and S.Z.; Formal analysis: Y.F. and W.S.; Methodology: A.R. and M.L.; Writing – original draft: M.H. and S.Z.; Writing – review and editing: Y.F. and W.S. All authors have read and agreed to the published version of manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Supplementary Materials

The following supporting information can be downloaded at: <https://ojs.exploverpub.com/index.php/jecacm/article/view/184/sup>. Supplementary Material 1: A list of ingredients and targets. Supplementary Material 2: A list of CRC genes. Supplementary Material 3: A list of Network proximity.

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