Traditional Chinese Medicine in colorectal cancer treatment: a bibliometrics study and visualization analysis via CiteSpace

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Author contributions
Wen-Kai Wang and Yuan-Yuan Feng conceptualized and wrote the manuscript. Yi-Yang Zhao and Zi-Wei Wang edited the critical revisions. Chao-Wei Wang carried out the painting of graphics. Xue-Qing Hu guided article writing. Ling Bi and Yan Wang provided supervision of the entire manuscript. All authors approved the final version of the manuscript for submission.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
TCM, Traditional Chinese medicine; CRC, Colorectal cancer; EMT, epithelial-mesenchymal transition.

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Abstract
Objective: To evaluate the current state of research and areas of interest for traditional Chinese medicine (TCM) in the field of colorectal cancer treatment. Methods: Related papers published between January 1, 2012, and November 27, 2021, were found using the Web of Science Core Collection Science Citation Index Expanded. Using CiteSpace’s network map generation capability, we then determined the top writers, organizations, countries, keywords, co-cited writers, journals, references, and research trends. Results: This investigation yielded a total of 336 relevant papers. China is the most productive country. Shanghai University of Traditional Chinese Medicine is the leading institution. The journal with the most popularity and publishing volume is Evidence-based Complementary and Alternative Medicine. The author with the most citations and centrality is Lin JM. The terms "epithelial-mesenchymal transition," "cell cycle arrest," "apoptosis," and "autophagy" are highly frequent and have a high betweenness centrality. Conclusion: According to the results, research on natural products, traditional Chinese medicine (TCM) extracts, and the molecular mechanisms of TCM chemical constituents constitutes the primary focus within TCM cancer treatment investigations. In recent years, there has been a surge of interest in exploring the role of gut microbiota in TCM chemical constituents research, particularly in its ability to induce apoptosis and autophagy in tumor cells, thereby suppressing tumor cell proliferation, metastasis, and invasion. However, due to the intricate composition of TCM and existing technical limitations, the underlying principles guiding TCM’s efficacy in treating colorectal cancer remain unclear and warrant further investigation.

Keywords: colorectal cancer; Traditional Chinese Medicine; bibliometrics study; visualization analysis; CiteSpace
Colorectal cancer (CRC) is a common malignant disease, usually caused by aberrant epithelial cell proliferation in the colon or rectum [1]. About 30%-35% of all rectal cancers are caused by colorectal cancer, the third most common cancer worldwide [2]. Even with recent improvements in surgery, radiotherapy, and chemotherapy, CRC continues to be the main cause of cancer-related death [3, 4]. The major management strategy for CRC is presently laparoscopic colorectal resection [5]. Recurrence and metastatic spread of the disease continue to be the leading causes of CRC mortality, despite recent improvements in CRC treatment that have considerably improved clinical outcomes for patients with advanced CRC [6]. CRC has been successfully treated with a variety of chemotherapy regimens over the years, but more innovative therapeutic drugs must still be developed [7].

For more than 2,000 years, Traditional Chinese Medicine (TCM) has used herbs and herbal extracts to treat a range of illnesses [8]. Based on TCM principles, traditional Chinese medicines have been utilized to treat cancers such as breast carcinoma, gastric cancer, and colorectal cancer using prescriptions that are thought to target numerous pathways [9]. The Chinese National Medical Insurance Catalogue (2017) divides TCMs for oncology treatment into two categories: adjuvant TCM for tumors and antitumor TCM, which all contain 40 TCM prescriptions [10].

TCM is commonly used in the treatment of CRC. For example, Jiedu Sangen Decoction, which has been used for more than 50 years to treat CRC, has the power to prevent CRC cells from migrating and invading [11]. Compound-composed optimal formula was generated by Aidi injection, which decreased mitochondrial membrane potential, enhanced cytochrome c leakage of hepatocellular carcinoma and CRC cells, raised the number of dead cells, increased apoptosis, and prevented tumor growth in nude mice having hepatocellular carcinoma(HCC) and CRC [12]. Wei Chang'An formula (WCAF) has been shown to be effective against subcutaneous xenografts of the human colon cancer HCT-116 in nude mice by inhibiting tumor development, promoting apoptosis, and reducing tumor angiogenesis. By blocking VEGFR-1, WCAF also compensates for Bevacizumab’s shortcomings [13]. By activating the Nrf2 pathway and increasing the production of Nrf2-downstream phase II enzymes, Shaoyao decoction helps enhance antioxidant capacity and helps prevent and treat CRC associated with ulcers [14].

Through information visualization, bibliometric analysis can forecast the hotspots and trends within a specific study field [15]. Metrology aspects and data from online literature databases were examined using bibliometric analysis, which may be used to assess statistically and qualitatively the trends in the research community over time. [16]. This kind of study can contrast the contributions of various nations, institutions, publications, and researchers in addition to describing and forecasting development in a particular research subject [17].

By using bibliometric analysis, we aimed to show the advancements and trends of TCM in CRC research over the past 10 years. Furthermore, our study could serve as a reference for researchers to track research hotspots and guide research direction.
There were 16 author clusters (Figure 2B) produced by log-likelihood ratio, mainly around Pien tze huang, Shenmai injection, postoperative stage, cinnamomum verum component cuminaldehyde, spica prunellae, bcl-2 signaling pathway, liver-kidney syndrome, Shi-re syndrome, oxaliplatin-resistant Lovo colorectal cancer cell, modulating matrix metalloproteinases, orthotopic transplantation, abcd1-mediated drug resistance, Chinese American community. The silhouette of all clusters is over 0.9, indicating clusters are efficient and convincing.

The lines link the authors, who are represented by the nodes. The number of publications increases in direct proportion to the node size. The lines connecting the nodes represent the cooperation relationships, with the thickness of the lines indicating the strength of collaboration; thicker lines signify stronger cooperation. Nodes encircled in red denote higher centrality within the network. Additionally, a color gradient shift from blue to red is observed between 2012 and 2021, indicating changes in collaboration dynamics over time.

Author and journal co-citation
Figure 3A shows the co-cited author network; the authors with the highest number of co-citations are represented by the most noticeable nodes, which include Siegel RL (57 Citation), Jemal A (35 Citation), and Liu JM (34 Citation) (Table 2). Besides, Lin JM was also a high-centrality author. The top-5 ranked authors by citation counts are listed in Table 2.

A Cancer Journal for Clinicians was top-ranked with 168 citations, followed by PLOS ONE (151 citations), Journal of Ethnopharmacology (149 citations), Cancer Research (128 citations), Evidence-based Complementary and Alternative Medicine (127 citations) (Figure 3B). Both Cancer Letter and Evidence-based Complementary and Alternative Medicine are among the top 10 journals in terms of both high frequency and high betweenness centrality, highlighting their pivotal role within this field.

According to Table 3, the initial co-cited reference, authored by Bray F et al., offers a statistical report on the global cancer burden [18]. This reference serves as a foundational piece within the network of co-cited references. The references published by Zhuang QC et al., Shen AL et al., and Lin JM et al. all introduced the therapeutic effect of Pien Tze Huang on colorectal cancer. Among them, references published by Shen AL et al., and Lin JM et al. got relatively high centrality, indicating its representativeness (Figure 4A). Figure 4B shows the clusters of reference.

The top 19 references with the strongest citation bursts were displayed in Figure 5, which represents recent research trends or increasing interests in the field.

Table 1 The 5 most productive author

<table>
<thead>
<tr>
<th>Rank</th>
<th>First author</th>
<th>Country</th>
<th>No. of publications</th>
<th>Centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PENG J</td>
<td>China</td>
<td>37</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>CHEN Y</td>
<td>China</td>
<td>33</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>LIN J</td>
<td>China</td>
<td>28</td>
<td>0.11</td>
</tr>
<tr>
<td>4</td>
<td>WANG Y</td>
<td>China</td>
<td>25</td>
<td>0.04</td>
</tr>
<tr>
<td>5</td>
<td>LIU L</td>
<td>China</td>
<td>21</td>
<td>0.22</td>
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</table>

Figure 2 The graphic representation of the CiteSpace network of authorship and co-authorship clusters related to TCM for CRC treatment. (A) The collaboration network. (B) The authorship cluster network.

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Figure 3. A graphic representation of the CiteSpace network of co-cited authors and journals related to TCM for CRC treatment. (A) The author co-citation network. (B) The journal co-citation network. The lines link the nodes, which stand in for writers or journals. The size of the nodes directly correlates with the frequency of co-citations by authors or journals. The cooperation relationship is represented by the lines connecting nodes, and the strength of that cooperation is indicated by the thickness of the connecting lines; the stronger the cooperation, the thicker the connecting lines. Higher centrality is found in the nodes with the red circles around them. The color changes from blue to red between 2012 and 2021.

Table 2. The top-5-ranked authors by citation count

<table>
<thead>
<tr>
<th>Rank</th>
<th>Author</th>
<th>Frequency</th>
<th>Centrality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Siegel RL</td>
<td>57</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>Jemal A</td>
<td>35</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>Lin JM</td>
<td>34</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>Bray F</td>
<td>31</td>
<td>0.08</td>
</tr>
<tr>
<td>5</td>
<td>Chen WQ</td>
<td>28</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 3. The top-5-ranked authors by citation counts

<table>
<thead>
<tr>
<th>Rank</th>
<th>First author</th>
<th>Frequency</th>
<th>Country</th>
<th>Centrality</th>
<th>Journal</th>
<th>Cited Reference</th>
<th>IF</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bray F</td>
<td>31</td>
<td>USA</td>
<td>0.01</td>
<td>CA-A Cancer Journal for Clinicians</td>
<td>Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries</td>
<td>286.13</td>
<td>2018</td>
</tr>
<tr>
<td>2</td>
<td>Jemal A</td>
<td>21</td>
<td>USA</td>
<td>0.01</td>
<td>CA-A Cancer Journal for Clinicians</td>
<td>Cancer statistics, 2010</td>
<td>286.13</td>
<td>2011</td>
</tr>
<tr>
<td>3</td>
<td>Chen WQ</td>
<td>20</td>
<td>China</td>
<td>0.05</td>
<td>CA-A Cancer Journal for Clinicians</td>
<td>Cancer statistics in China, 2015</td>
<td>286.13</td>
<td>2016</td>
</tr>
<tr>
<td>4</td>
<td>Zhuang QC</td>
<td>12</td>
<td>China</td>
<td>0.04</td>
<td>International Journal of Oncology</td>
<td>Pien Tze Huang inhibits tumor cell proliferation and promotes apoptosis via suppressing the STAT3 pathway in a colorectal cancer mouse model</td>
<td>5.88</td>
<td>2012</td>
</tr>
<tr>
<td>5</td>
<td>Siegel R</td>
<td>12</td>
<td>USA</td>
<td>0.02</td>
<td>CA-A Cancer Journal for Clinicians</td>
<td>Colorectal cancer statistics, 2017</td>
<td>286.13</td>
<td>2017</td>
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Advances is India network (Figure demonstrates and the network greatly ranked the University, clusters reference the of top identification merged associated the research promotes proliferation, items the to between indicated (A) exhibiting University by got Chinese of Medicine co-institution that strongest TCM, of of Shanghai generalization the and merged between analysis strongest of It keywords. Followed Traditional Medicine Institutions and countries

The merged co-institution network is presented in Figure 6A. In terms of the number of publications, Shanghai University of Traditional Chinese Medicine (46) is the highest, followed by Fujian University of Traditional Chinese Medicine (39 publications), Nanjing University of Chinese Medicine (17 publications), Case Western Reserve University (17 publications) and China Medicine University (17 publications). The betweenness centrality of Shanghai University of Traditional Chinese Medicine, China Medicine University, and Zhejiang Chinese Medicine University was over 0.9.

China has the most publications (325 publications) associated with colorectal cancer which is treated by TCM, followed by the United States of America (USA) (42 publications). China (1.28), the USA (0.37), and India (0.19) got the highest centrality (Figure 6B), illustrating significant contributions of the field.

Keywords co-citation and clusters

A piece of writing's high level of generalization is its keywords. The most popular research topics in this field are typically reflected in the high-frequency and high-centrality keywords. Following a one-year time-slicing analysis of publications and the identification of the top 30 most-cited or occurred items from each slice, Figure 7A showcases the merged co-occurring keywords network. The analysis yielded 15 clusters identified by log-likelihood ratio, encompassing themes such as tumor cell proliferation, BCL-2 signaling pathway, 5-fluorouracil resistance, and others (Figure 7B).

Keywords with citation bursts

Figure 8 displays the top 14 keywords exhibiting citation bursts. The keyword “network pharmacology” (strength 6.76) with the strongest citation burst appeared in 2020. It provides a new method for the study of TCM and greatly promotes the progress of pharmacological research on TCM. The keyword “natural product” (strength 5.68) appeared in 2012 and also got a strong citation burst.

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Figure 4 A visual map for the CiteSpace network of co-cited reference and co-cited reference clusters associated with TCM in the treatment of CRC. (A) The network of reference co-citation illustrates connections between nodes, each representing the institution of first authors of co-cited references. The network of co-cited reference clusters demonstrates relationships between nodes, where each node symbolizes the country of first authors of co-cited references. The number of nodes increases in direct proportion to the frequency of reference co-citation. The cooperation relationship is represented by the lines connecting the nodes, and the strength of that cooperation is indicated by the thickness of the connecting lines; the stronger the cooperation, the thicker the connecting lines. Higher centrality is found in the nodes with the red circles around them. From 2012 to 2021, the color changes from blue to red.

Figure 5 Top 19 References with the strongest citation bursts

<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>Start</th>
<th>End</th>
<th>2012 - 2022</th>
</tr>
</thead>
<tbody>
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<td><strong>Chinese pharmacopoeiaaccommision, 2010, PHARMACOPOEA PEOPLE, V1, P573</strong></td>
<td>2010</td>
<td>2.71</td>
<td>2012</td>
<td>2015</td>
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<tr>
<td>Siegel RL, 2015, CA - CANCER J CLIN, V65, P5, DOI: 10.3322/cac.21254, DOI</td>
<td>2015</td>
<td>2.65</td>
<td>2017</td>
<td>2019</td>
</tr>
<tr>
<td>Dekker E, 2019, LANCET, V394, P1467, DOI: 10.1016/S0140-6736(19)32319-0, DOI</td>
<td>2019</td>
<td>2.59</td>
<td>2020</td>
<td>2022</td>
</tr>
</tbody>
</table>
Figure 6 A visual map for the CiteSpace network of Institutions and countries associated with TCM in the treatment of CRC. (A) The network of co-institution. (B) The network of co-country. The lines link the nodes, which stand for organizations or nations. Nodes stand in for organizations or nations. The number of publications increases in direct proportion to the node size. The cooperation relationship is represented by the lines connecting the nodes, and the strength of that cooperation is indicated by the thickness of the connecting lines; the stronger the cooperation, the thicker the connecting lines. Higher centrality is found in the nodes with the red circles around them. From 2012 to 2021, the color changes from blue to red.

Figure 7 A visual map for the CiteSpace network of co-cited keyword and co-cited keyword clusters associated with TCM in the treatment of CRC. (A) The network of co-cited keywords. (B) The network of co-cited keyword clusters. The lines link the nodes, which stand for keywords. Keywords are represented by nodes. The size of the nodes has a direct correlation with the frequency of keyword co-citation. The cooperation relationship is represented by the lines connecting the nodes, and the strength of that cooperation is indicated by the thickness of the connecting lines; the stronger the cooperation, the thicker the connecting lines. Higher centrality is found in the nodes with the red circles around them. From 2012 to 2021, the color changes from blue to red.

Figure 8 The Top 14 Keywords for Citation Burst Power
Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Discussion
We compiled the most recent findings on the molecular mechanism of TCM's treatment of colorectal cancer based on CiteSpace's results, which include the following.

Inhibiting epithelial-mesenchymal transition (EMT)
Ursolic acid which was isolated from Hedysotis diffusifolia/Barbara/Prunus prunus/Paniculata has the potential to suppress epithelial-mesenchymal transition (EMT) and the invasion of colorectal cancer (CRC) cells by modulating the TGF-β1/ZEβ1/miR-200c signaling pathway [19]. Solanine which is isolated from solanum can suppress stemness and EMT in colon cancer. In vitro and in vivo, studies have demonstrated that Solanine, isolated from Solanum, can effectively suppress both stemness and EMT in colon cancer cells [20]. Apigenin, berberine, and paeoniflorin can effectively inhibit the metastasis of colon cancer through different signal pathways to EMT [21–23]. Nerisigone has been shown to inhibit the migration of colorectal cancer cells by arresting the cell cycle in the G2/M phase and suppressing the ERK/GSK3β/β-catenin signaling pathway through its inhibition of EMT [24].

According to the network of co-cited references, the TGF-β pathway is a hotspot. For example, Resveratrol often serves as an EMT inhibitor, which isn’t a flavonoid, was taken out of Veratrum grandifolium (Maxim. ex Miq.) O. Loes. Resveratrol has been shown by Qing Ji et al. to inhibit the metastasis of orthotopic colon tumors in mice as well as the cell metastasis of mice injected with colorectal cancer cells via the tail vein. Research on cell function revealed that Resveratrol inhibits TGF-β1-induced EMT via the Smads signaling pathway [25]. Furthermore, it was discovered by Li Yuan et al. that resveratrol could inhibit EMT through the AKT/GSK3β/Snail signaling pathway [26].

Inducing apoptosis
According to a report, Jianpi Jiedu decoction inhibits colorectal cancer invasion by inducing apoptosis via the mTOR/HDAC-1/VEGF pathway [27]. Furthermore, Jianpi Jiedu decoction is a common clinical treatment for colorectal cancer, often administered in conjunction with other medications, resulting in improved patient prognosis [28]. Zuo Jin Wan extracts have the potential to incite apoptosis and cause cell cycle arrest in G1 by blocking the Wnt/β-catenin signaling pathway [29].

Dehydrocostus has been found to induce cell apoptosis, trigger cell cycle arrest in the G0/G1 phase, and inhibit the proliferation and migration of colorectal cancer cells [30]. By inducing cell apoptosis, podophyllotoxin, and colchicine—all derived from Coptidis coptidis Franch—can prevent colon cancer from proliferating and invading the tissue [31, 32]. Cell cycle arrest at G0/G1 phases and apoptosis are caused by Radix Tetrassiga hemsleyani flavone, which is extracted from Tetrastigma hemsleyanum [33]. Betulinic acid uses mitochondria-mediated apoptosis to prevent colorectal cancer from migrating [34].

Inducing autophagy
Autophagy plays a crucial role in cellular metabolism and is an important mechanism in tumor development [35, 36]. In colorectal cancer, autophagy can either increase tumor survival or cause cancer cell death. A better understanding of the potential connections between TCM and autophagy is essential given that autophagy is involved in the treatment of colorectal cancer. According to certain research, T33 (a TCM formula) caused autophagy-induced cell death in HT-29 and Caco2 cells, suggesting that T33’s therapeutic effects in the treatment of CRC are mediated by excessive autophagy [37]. The polysaccharide derit fraction (DBT-PD) of Angelica Buxu Tang has the potential as a chemotherapy or radiotherapy sensitizer in colorectal cancer by inducing autophagy-associated cell death in CT26 cells [38]. From Rubia yunnanensis Diels, the bicyclic hexapetide glucoside RA-XII was identified. In CRC-associated SW620 and HT29 cell lines, RA-XII reduced protective autophagy while also exerting anticancer activity that was independent of apoptosis [39]. While components in other herbal medicines, such as artemisin, inhibit cell proliferation in colorectal cancer by promoting excessive ROS generation to induce senescence and autophagy [40].

Suppressing proliferation, migration and invasion
Cell growth is significantly influenced by cell proliferation, migration, invasion, and death [41]. The development of CRC is closely related to the proliferation, migration, and invasion of cancer cells. According to a different study, concentration-dependent inhibition of CT-26 cells' ability to migrate, invade, and undergo EMT is possible when Jiedu Sangen Decoction (JSD) and PD-L1 inhibitor are used together [42]. Jianpi Jiedu decoction inhibits anti-colorectal tumor cell migration, invasion, and angiogenesis through inhibition of the mTOR/HIF-1α/VEGF pathway [27]. The STAT3 expression was significantly decreased in CRC cells after diosgenin treatment. The inhibition of colon cancer cell migration and proliferation by 50 mol/L diosgenin would be reversed by the overexpression of STAT3, which would also increase apoptosis [43]. Sanghuangporus vuninii was used as the source of inoscin A using the traditional phytochemical separation method. According to a study, inoscin A's anti-cancer activities were manifested via decreasing Smo, which in turn suppressed the activity of the hedgehog pathway by preventing CRC cells from proliferating and encouraging apoptosis [44].

Prospects and challenges of TCM in CRC
TCM presents numerous prospects and challenges in the treatment of CRC. The prospects include its rich historical background and extensive clinical experience, as well as therapeutic effects demonstrated in certain studies. TCM, with its unique theoretical framework and comprehensive treatment methods, may play a positive role in the treatment of colorectal cancer. For instance, it may enhance immune function, slow disease progression, or alleviate symptoms by adjusting the overall balance within the patient's body [8].

However, TCM also faces several challenges in the treatment of colorectal cancer. Firstly, the mechanisms of action of TCM in modern medicine are not fully understood, making it difficult to integrate into standard treatment protocols. Secondly, due to limitations in the quantity and quality of clinical research, evidence regarding the efficacy of TCM in colorectal cancer treatment is insufficient, lacking support from large-scale clinical trials. Additionally, personalized treatment plans with TCM pose challenges as individualized approaches tailored to each patient's specific condition may be more complex to formulate.

Therefore, despite the potential prospects of TCM in colorectal cancer treatment, further clinical research is necessary to validate its efficacy and address the challenges it faces. This will ultimately enable better treatment options for patients.

Conclusion
This study analyzed the research hotspots and trends of TCM in the treatment of colorectal cancer via CitSpace. According to the findings, research on natural products, extracts of traditional Chinese medicine (TCM), and the molecular mechanisms of TCM chemical monomers are extensively explored in cancer treatment. Additionally, in recent years, there has been a surge of interest in investigating the role of gut microbiota in TCM chemical monomers research. These monomers have demonstrated the ability to induce apoptosis and autophagy in tumor cells, effectively suppressing tumor cell proliferation, metastasis, and invasion. However, due to the complex composition of TCM and the existing technical limitations, the principle of TCM in the treatment of CRC has not been clarified, which needs to be further studied.
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