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Analysis

Crosstalk between gut microbiota and cancer chemotherapy: current status and trends

Shanshan Yang[1] · Shaodong Hao[2] · Hui Ye[1] · Xuezhi Zhang[1]

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Abstract

Background Chemotherapy is crucial in the management of tumors, but challenges such as chemoresistance and adverse reactions frequently lead to therapeutic delays or even premature cessation. A growing body of research underscores a profound connection between the gut microbiota (GM) and cancer chemotherapy (CC). This paper aims to pinpoint highly influential publications and monitor the current landscape and evolving trends within the realm of GM/CC research.

Methods On October 1st, 2024, a comprehensive search for GM/CC publications spanning the past 20 years from 2004 to 2023 was conducted utilizing the Web of Science Core Collection (WoSCC). The scope encompassed both articles and reviews, and the data was subsequently extracted. To gain insights into the evolution and dynamics of this research field, we employed bibliometric analysis tools such as the Bibliometrix R package, VOSviewer, and Microsoft Excel to visualize and analyze various dimensions, including prominent journals, leading authors, esteemed institutions, contributing countries/regions, highly cited papers, and frequently occurring keywords.

Results A total of 888 papers were obtained. The number of publications about GM/CC studies has increased gradually. China and the United States published the largest number of papers. The *INSERM* was in the leading position in publishers. The most productive authors were Zitvogel L from France. *Cancers* had the largest number of papers. Citation analysis explained the historical evolution and breakthroughs in GM/CC research. Highly cited papers and common keywords illustrated the status and trends of GM/CC research. Four clusters were identified, and the hot topics included the role of the GM in the efficacy and toxicity of CC, the targeting of the GM to improve the outcome of CC, the mechanism by which the GM affects CC, and the correlation of the GM with carcinogenesis and cancer therapy. Metabolism, GM-derived metabolites, tumor microenvironment, immunity, intestinal barrier, tumor microbiota and *Fusobacterium nucleatum* may become the new hotspots and trends of GM/CC research.

Conclusion This study analyzed global publications and bibliometric characteristics of the links between GM and CC, identified highly cited papers in GM/CC, provided insight into the status, hotspots, and trends of global GM/CC research, and showed that the GM can be used to predict the efficacy and toxicity of CC and modifying the GM can improve the outcomes of chemotherapeutics, which may inform clinical researchers of future directions.

Keywords Chemotherapy · Gut microbiota · Cancer · Research trends · Highly cited papers · Bibliometrics

Abbreviations

GM	Gut microbiota
CC	Cancer chemotherapy
WoSCC	The Web of Science Core Collection

✉ Hui Ye, yehui@pkufh.cn; ✉ Xuezhi Zhang, zhang.xuezhi@263.net | [1]Department of Traditional Chinese Medicine, Peking University First Hospital, Beijing, China. [2]Spleen-Stomach Department, Fangshan Hospital, Beijing University of Chinese Medicine, Beijing, China.

IF	Impact factor
JCR	Journal citation report
5-FU	5-Fluorouracil
GI	Gastrointestinal
CRC	Colorectal cancer
ESCC	Esophageal squamous cell carcinoma
ROS	Reactive oxygen species
SCP	Single country publication
MCP	Multiple countries publications
TC	Total citations
H-index	Hirsch index
SCFAs	Short-chain fatty acids
TME	Tumor microenvironment
TM	Tumor microbiota

1 Introduction

Cancer continues to pose a significant global public health concern, with an estimated 19.3 million new cases and nearly 10 million deaths worldwide in 2020, and this trend is showing an increasing pattern [1]. Over the past century, significant advancements have been achieved in cancer chemotherapy (CC), leading to substantial improvements in patient survival rates. Nonetheless, a subset of cancer patients may encounter drug resistance and adverse effects during CC, thereby impeding the effective utilization of chemotherapy medications. The gut microbiota (GM), a complex community of microorganisms residing in the human intestine, has emerged as a crucial factor influencing various physiological and pathological processes, including cancer development and progression. In recent decades, an increasing number of studies, including preclinical and clinical studies, have shown that the GM and its metabolites can modulate the efficacy and toxicity of chemotherapeutics [2, 3]. The GM can serve as a biomarker to predict the therapeutic response and prognosis of cancer patients [4]. This crosstalk between GM and CC has the potential to revolutionize our understanding of cancer therapy and patient outcomes. As such, a comprehensive and systematic analysis of the existing research in this field is both timely and crucial.

Bibliometrics has been widely used in medical research, which can evaluate the quality and recognition of papers and determine the discipline construction and development trend of a field. Many related areas have been well-researched through bibliometric analysis [5, 6]. However, currently, no studies on the bibliometric analysis of interactions between the GM and CC have been published. In this analysis, we aim to map out the landscape of research on the crosstalk between GM and CC. By employing bibliometric methods, we will examine trends in publication output, citation patterns, key researchers, and institutions that have contributed to this field. Additionally, we will explore the most frequently used keywords and research themes, providing insights into the evolving focus and priorities of GM/CC research. By shedding light on the interconnectedness between gut microbiota and cancer chemotherapy, we hope to pave the way for future research that can harness this crosstalk to improve cancer treatment outcomes and enhance patient quality of life. Specifically, we aim to address the following issues: (1) How have research efforts in this field evolved over time, and what are the key milestones and breakthroughs that have shaped the current landscape? (2) What are the potential mechanisms by which the GM may influence the efficacy and toxicity of CC? (3) What are the main limitations and challenges in the current research on GM/CC, and how can these be addressed in future studies? (4) What are the clinical implications of these findings, and how can they be translated into improved patient outcomes?

2 Materials and methods

2.1 Data sources and search methods

The WoS database is renowned and reliable as a citation index, attributed to its rigorous criteria for evaluating and selecting journals, as well as its ability to furnish accurate and trustworthy information [7]. The Science Citation Index Expanded (SCIE) of WoSCC includes the most influential academic journals and was used as the search source. This study used a similar method to Gholampour et al.'s method to identify articles relevant to the study, so the search strategy used in this study reflects the approach of Gholampour et al. [5, 6]. All searches were performed, and the data were retrieved on the

same day (Oct 1st, 2024). The "advanced search" was used, and the search terms used were TI or AK or AB = "chemotherapy" and "gut microbiome" and "cancer", and their corresponding synonyms (Table 1). The selection criteria were as follows: (1) The search period ranged from January 1, 2004, to December 31, 2023, when the most recent research progress and trends were obtained, and the accuracy and reliability of the citation data were ensured to carry out citation analysis and evaluation better. (2) The paper types were "article" and "review". We browsed the title and abstract of the articles and excluded articles unrelated to chemotherapy, such as cancer immunotherapy and cancer-targeted therapy. The search and data extraction were independently carried out by two researchers (SY and SH). After that, we refined the key information and saved it in text format.

2.2 Data analysis and parameter query

Bibliometric analysis was conducted with the aid of the Bibliometrix (https://www.bibliometrix.org), VOSviewer 1.6.18 (Centre for Science and Technology Studies, Leiden University, the Netherlands), and Microsoft Excel 2021. VOSviewer was used for visualizing relational networks and for performing a cluster analysis of keywords. Bibliometrix and Excel were used for quantitative research. We used the following variables: annual paper production, journal dynamics, most local impact journals according to the H-index (the H-index of a journal is defined as the largest number h such that the journal has published h papers that have each been cited at least h times) or total citations (TC), which can indicate the academic importance of the journals, top journal production over time, top authors and their production

Table 1 Search query and refinement procedure

Set	Results	Refinement
1	1226	Query formulation: Step 1: #1 TI OR AB OR AK = ("Tumor*" OR "Tumour*" OR "Cancer*" OR "Neoplasia*" OR "Neoplasm*" OR "Malignanc*" OR "Carcinoma*" OR "Oncolog*" OR "Melanoma*" OR "Lymphoma*" OR "Scrcoma*" OR "Adenocarcinoma*" OR "Leukemia*" OR "Myeloma*" OR "Blastoma*" OR "Glioma*") Step 2: #2 TI OR AB OR AK = ("Gut Microb*" OR "Gut Microflora" OR "Gut Flora" OR "Gut Microbial Flora" OR "Gut Microecology" OR "Intestinal Microb*" OR "Intestinal Microflora" OR "Intestinal Flora" OR "Intestinal Microbial Flora" OR "Intestinal Microecology" OR "Gastrointestinal Microb*" OR "Gastrointestinal Microflora" OR "Gastrointestinal Flora" OR "Gastrointestinal Microbial Flora" OR "Gastrointestinal Microbial Communit*" OR "Gastrointestinal Microecology" OR "Fecal Microb*" OR "Fecal Microflora" OR "Fecal Flora" OR "Fecal Microbial Flora" OR "Faecal Microb*" OR "Faecal Microflora" OR "Faecal Flora" OR "Faecal Microbial Flora" OR "Gut Bacteri*" OR "Intestinal Bacteri*" OR "Gastrointestinal Bacteri*" OR "Gut Dysbiosis" OR "Intestinal Dysbiosis" OR "Gastrointestinal Dysbiosis" OR "Fecal Bacteri*" OR "Faecal Bacteri*" OR "Enteric Bacteri*" OR "Commensal Bacteri*" OR "Commensal Fungi" OR "Commensal Microb*" OR "Microb* Metaboli*" OR "Bacteri* Metaboli*") Step 3: #3 TI OR AB OR AK = ("Chemothera*" OR "Chemical therap*" OR "Chemical treat*" OR "Alkylating agent*" OR "Cyclophosphamide" OR "Isophosphamide" OR "Temozolomide"OR "Platinum" OR "Cisplatin" OR "Oxaliplatin" OR "Carboplatin" OR "Nedaplatin" OR "Lobaplatin" OR "Anthracycline" OR "Doxorubicin" OR "Adriamycin" OR "Epirubicin" OR "Epidoxorubicin" OR "Bleomycin" OR "Mitomycin" OR "Fluoropyrimidine*" OR "Fluorouracil" OR "Flurouracil" OR "Floxuridine" OR "5-FU" OR "Capecitabine" OR "Cyclocytidine" OR "Cytarabine" OR "Gemcitabine" OR "Fludarabine" OR "Clartrobine" OR "Paclitaxel" OR "Docetaxel" OR "Vincristine" OR "Vinblastine" OR "Vindesine" OR "Vinorelbine" OR "Camptothecin" OR "Topotecan" OR "Irinotecan" OR "CPT-11" OR "Etoposide" OR "Teniposide" OR "Methotrexate" OR "Raltitrexed" OR "Pemetrexed" OR "Cytotoxic drug*" OR "Cytotoxic therap*" OR "Cytotoxic treat*" OR "Cytotoxic agent*" OR "Antimetabolite*" OR "Chemoresistance" OR "Chemosensitivit*") Step 4: #1 AND #2 AND #3 Indexes = SCI-EXPANDED
2	1149	Refined by document types: (articles and review articles)
3	1053	Exclude irrelevant literature (such as cancer immunotherapy, targeted therapy, etc.)
4	888	Refined by publication years: (2004–2023)

Query link: https://webofscience.clarivate.cn/wos/woscc/summary/59b34ff3-5e4e-47db-b39c-5312e31ed302-010e528e0c/times-cited-descending/1

and impact, top affiliations and funding agencies, country production and country collaboration network, historical direct citation network, highly cited papers, keywords and their cluster analysis (use statistical methods to discover latent themes or topics within a corpus of documents, aiding in the exploration of research landscapes). The impact factor (IF) and journal citation report (JCR) partition (calculate the average number of citations received by articles published in a journal over a specific period, reflecting the journal's prestige and influence) of published journals in 2023 can be found in the "2023 Journal Citation Report".

3 Results

3.1 Annual development trend

A total of 888 documents were identified, comprising 577 articles and 311 reviews. The number of papers (Np) can show the publication trend of GM/CC research. Figure 1 shows the annual and cumulative Np in GM/CC from 2004 to 2023, with an upward trend. According to the Np, we can find that the Np from 2004 to 2012 was very small, which demonstrates that relevant research is in its infancy. The Np from 2013 to 2018 increased slowly, showing that it is in the initial stage of development. From 2018 to 2021, the Np increased rapidly in the stage of rapid development. From 2021 to 2023, the growth tended to be flat.

3.2 Main journals in GM/CC research

A total of 412 journals published papers on GM/CC research. Table 2 shows the top 10 prolific journals in the Np. *Cancers* had the highest Np (n = 40), followed by the *International Journal of Molecular Sciences* (n = 28), *Frontiers in Oncology* (n = 12), *Nutrients* (n = 15), and *Scientific Reports* (n = 15). Moreover, in the top 10 highly prolific journals, *Cancers* had the highest H-index (H = 17), followed by *International Journal of Molecular Sciences* (H = 15), the *Journal of Global Antimicrobial Resistance* (H = 10), and *Biomedicine & Pharmacotherapy* (H = 10). Figure 2A depicts the annual Np of the top 10 prolific journals, of which *Nutrients* and *the Journal of Global Antimicrobial Resistance* started earliest, and *Cancers* had

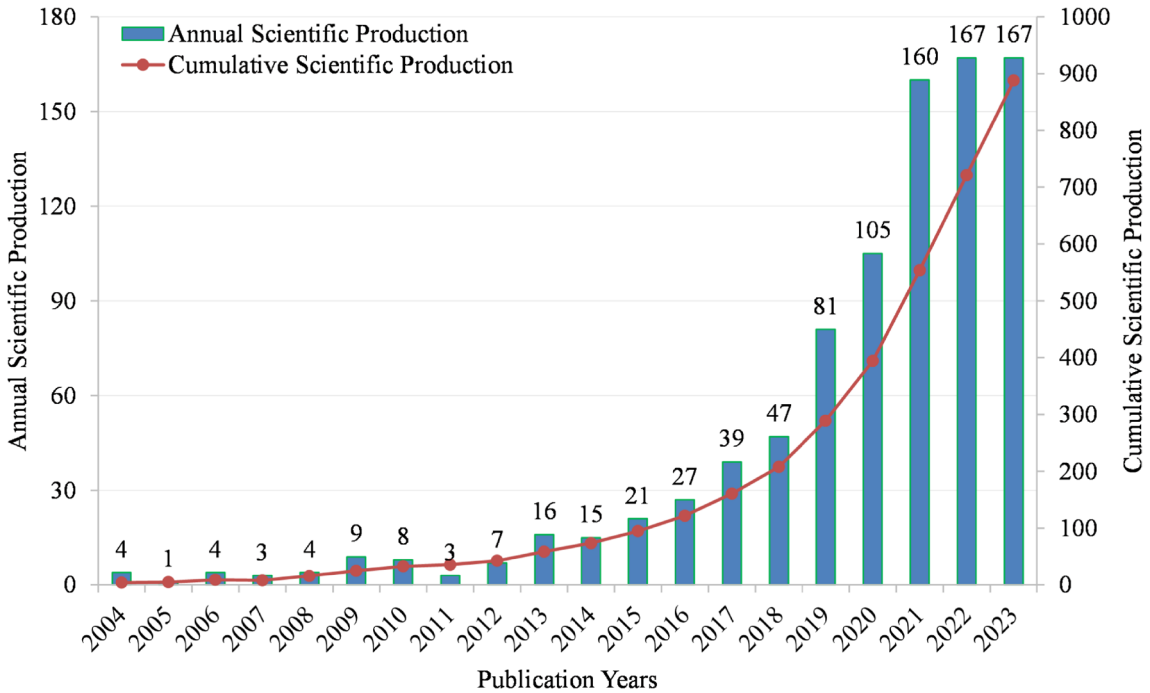

Fig 1. Annual and cumulative manufacturing output in GM/CC (the bar chart shows annual scientific production, whereas the line chart shows cumulative production)

the fastest growth rate. Figure 2B summarizes the cumulative Np in the top 10 prolific journals. There were 174 papers in these journals, accounting for approximately 19.59% of all the papers.

3.3 Main authors in GM/CC research

The dataset includes 5455 authors. Table 3 lists the top 10 prolific authors, of which Zitvogel Laurence (n = 12), Weisdorf Daniel J. (n = 11), Rashidi Armin (n = 11), Staley Christopher (n = 10), Wardill Hannah R. (n = 10), Bowen Joanne M. M. (n = 10), Rehman Tauseef Ur (n = 10), Khoruts Alexander (n = 10) and Holtan Shernan G. (n = 10) had no less than 10 publications. Zitvogel L had the largest Np, the highest H-index and TC, indicating her great impact on GM/CC research. Figure 3A shows the change in scientific productivity of the top 10 authors' annual Np. Most of the authors' papers were published in 2020. Figure 3B shows the links of the top 20 prolific authors. Each node represents an author, and the lines represent collaboration networks between authors. We can find that Zitvogel L, Daillere R, and Kroemer G (team 1), Rashidi A, Weisdorf DJ, and Holtan SG (team 2), as well as Bowen J and Wardill HR (team 3) all exhibited the closest internal collaborations within their respective teams.

3.4 Main countries and affiliations in GM/CC research

These papers were distributed across 63 countries (Fig. 4A). Table 4 shows that the papers were published mainly in China (n = 308) and the United States (n = 202), accounting for about 57.4% of the total output, followed by Italy (n = 58), Japan (n = 53), and Australia (n = 42). An international collaboration analysis of the top countries was performed (Fig. 4A), and China had the closest link with USA. Figure 4B depicts the degree of collaboration of corresponding authors from the productive country, we can find that international cooperation in France was common. Figure 4C shows the annual Np of countries in terms of time distribution. We found that the United States, Italy, Japan began to study earlier, and China developed rapidly. China experienced a surge in annual Np and has outnumbered USA in recent years, which may be related to the increased amount of attention given to the GM program and CC research. Table 5 shows the top prolific institutions, of which *INSERM* (n = 28), *Peking Union Medical College* (n = 24), *Unicancer* (n = 21), *Chinese Academy of Sciences* (n = 20) and *Sun Yat-Sen University* (n = 18) were among the top five. Figure 4D depicts the main funding agencies such as the National Natural Science Foundation of China, the United States Department of Health Human Services, and the National Institutes of Health, which mainly were from China, USA, Japan, and Spain.

3.5 Historical direct cited papers in GM/CC research

Historiography analysis refers to the examination and interpretation of historical developments, trends, and patterns within a particular field or subject area, utilizing quantitative and qualitative methods derived from bibliometric data. This type of analysis allows researchers to understand how a field has evolved over time, identify key milestones, and recognize emerging trends or shifts in research focus. Using historiography analysis in the the Bibliometrix R

Table 2 Top 10 productive journals in GM/CC

No	Journals	Np	H-index	TC	IF	JCR	Countries
1	Cancers	40	17	1107	4.5	Q1	Switzerland
2	International Journal of Molecular Sciences	28	15	1637	4.9	Q1	Switzerland
3	Frontiers in Oncology	17	8	227	3.5	Q2	Switzerland
4	Scientific Reports	15	9	370	3.8	Q1	England
5	Nutrients	15	8	327	4.8	Q1	Switzerland
6	Journal of Global Antimicrobial Resistance	13	10	207	3.7	Q2	England
7	Frontiers in Microbiology	13	8	416	4	Q2	Switzerland
8	Biomedicine & Pharmacotherapy	12	10	431	6.9	Q1	France
9	Frontiers in Pharmacology	11	9	322	4.4	Q1	Switzerland
10	Food & Function	10	9	471	5.1	Q1	England

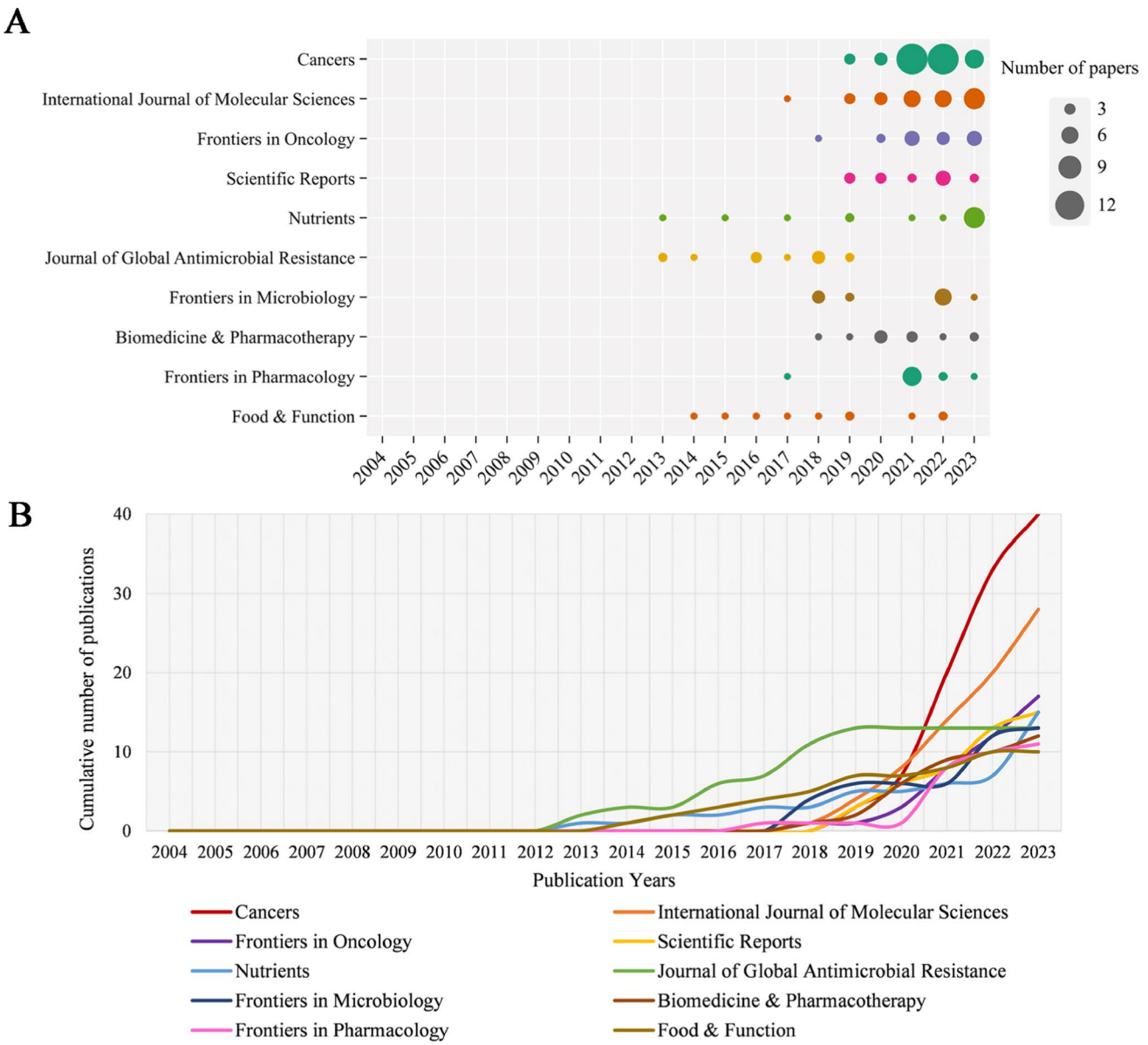

Fig 2. **A** The top 10 journals' annual publications in GM/CC (the size of the circle represents the number of publications; a larger circle indicates a greater quantity of publications). **B** The top 10 journals' cumulative publications in GM/CC

Table 3 The top 10 productive authors in GM/CC

No	Authors	Np	H-index	TC	Main Affiliations	Countries
1	Zitvogel, Laurence	12	11	3,004	Gustave Roussy	France
2	Rashidi, Armin	11	8	174	University of Minnesota	USA
3	Weisdorf, Daniel J	11	8	174	University of Minnesota	USA
4	Holtan, Shernan G	10	8	163	University of Minnesota	USA
5	Khoruts, Alexander	10	8	163	University of Minnesota	USA
6	Rehman, Tauseef-ur	10	8	163	NIH National Cancer Institute (NCI)	USA
7	Staley, Christopher	10	8	163	University of Minnesota	USA
8	Bowen, Joanne	10	8	697	University of Adelaide	Australia
9	Wardill, Hannah R	10	8	216	University of Adelaide	Australia
10	Kaiser, Thomas	9	8	157	University of Minnesota	USA

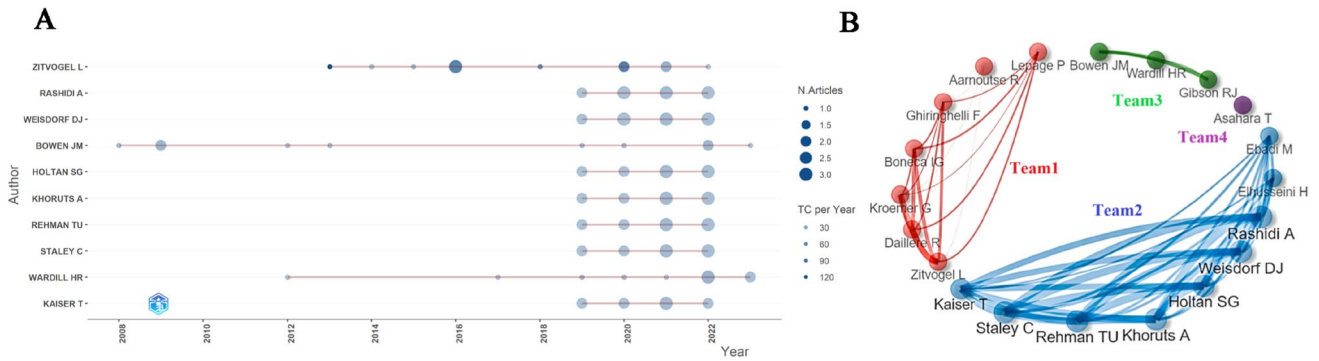

Fig 3. **A** The top 10 authors' annual production in GM/CC research (the size of the circle represents the number of papers, and the larger the circle is, the greater the number of papers; the depth of the circle represents the annual citations, and the darker the color is, the more citations there are). **B** The top 20 authors' cooperation networks in GM/CC research (the line represents the collaboration links between authors, and the thickness of the line represents the strength of collaboration; they are divided into different teams according to their cooperative relationship)

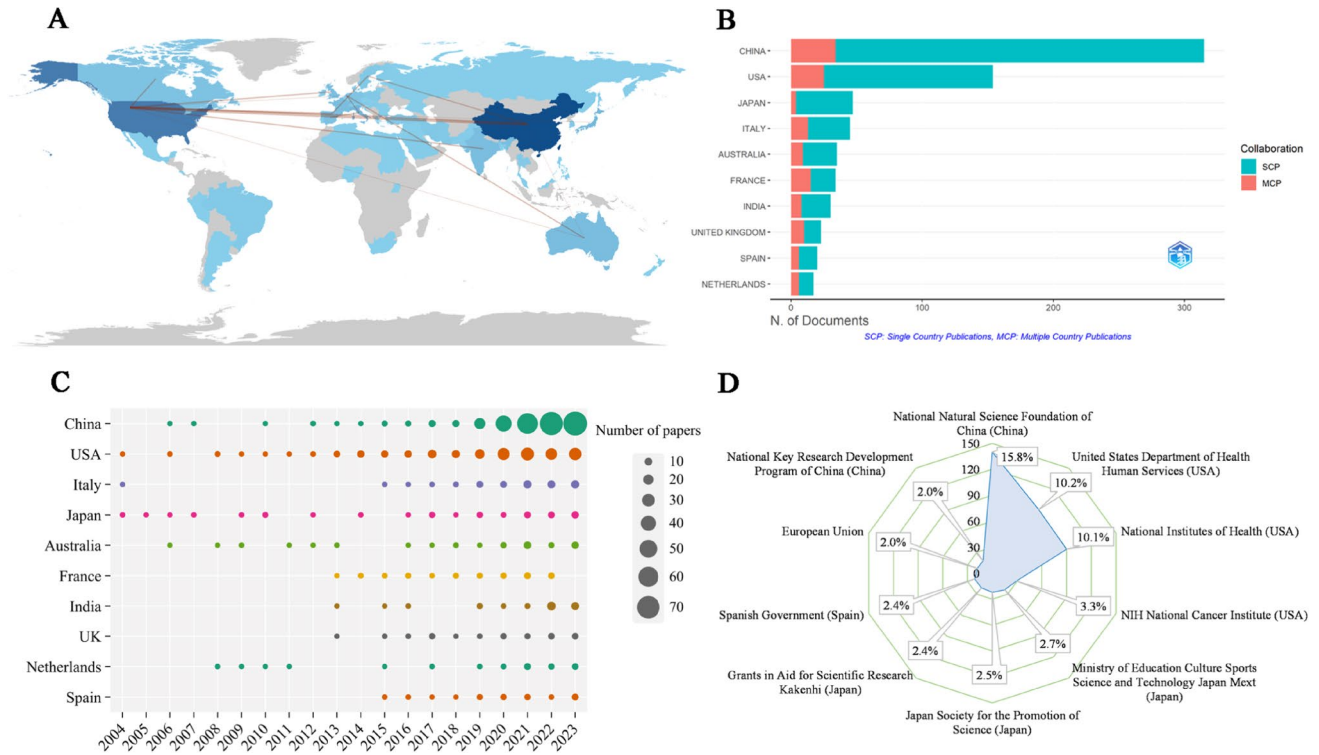

Fig 4. **A** Countries/regions scientific output and coordination relations in GM/CC (the colors in the image are composed of blue and gray, where gray represents countries/regions that have not published any documents, and blue varies in shade, with lighter blues indicating fewer published documents and darker blues indicating a higher number of published documents; the red lines depict the connections between countries, with thicker lines indicating closer connections and thinner lines indicating looser connections). **B** The nationality of correspondence authors and the rate of international cooperation in GM/CC (green SCP indicates the number of papers published by authors from the single country, and red MCP indicates the number of papers published by authors from multiple countries, MCP ratio shows the level of international cooperation). **C** The annual publications of top 10 prolific countries in GM/CC research (the size of the circle represents the number of publications; a larger circle indicates a greater quantity of publications). **D** The top 10 funding agencies in GM/CC research, including sources, countries and funding ratios

Table 4 The top 10 productive countries in GM/CC

Rank	Countries	Np	TC	H-index
1	China	308	10,082	49
2	USA	202	14,676	51
3	Italy	58	2,480	22
4	Japan	53	1,284	21
5	Australia	42	2,386	21
6	France	39	4,510	22
7	India	38	626	15
8	England	34	1,827	18
9	Netherlands	31	1,594	16
10	Spain	29	1,785	14

Table 5 The top 10 productive institutions in GM/CC

Rank	Institutions	Np	TC	H-index
1	Inserm (France)	28	3,868	19
2	Peking Union Medical College (China)	24	773	13
3	Unicancer (France)	21	3,280	16
4	Chinese Academy of Sciences (China)	20	459	13
5	Sun Yat-Sen University (China)	19	879	14
6	Universite Paris Cite (France)	19	3,165	15
7	Shanghai Jiao Tong University (China)	18	2,289	13
8	Universite Paris Saclay (France)	18	3,199	16
9	University of Adelaide (Australia)	17	935	11
10	University of Texas System (USA)	17	1,226	12

package (set the number of papers to 20) to construct a chronological network of the most relevant direct citations, we found some papers in the GM/CC research (Table 6).

The GM/CC correlation study initially focused on chemotherapy-induced diarrhea or mucositis. **In 2008**, Stringer et al. [8] showed that irinotecan increased the abundance of β-glucuronidase-producing bacteria such as *Escherichia coli*, *Staphylococcus* and *Clostridium* and decreased the abundance of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and an increase in β-glucuronidase-producing bacteria can aggravate the toxicity of irinotecan. **In 2009**, Stringer et al. [9] showed that 5-fluorouracil (5-FU) treatment can cause significant changes in GM and mucus secretion, which may lead to the development of CC-induced mucositis. Vliet et al. [10] reported that during chemotherapy, the total number of gut bacteria in patients decreased significantly, the balance between aerobic and anaerobic bacteria was disrupted, and these changes reduced resistance to pathogen colonization and increased the risk of gram-positive aerobic bacterial infection. **In 2010**, Wallace et al. [11] showed that the dose-limiting toxicity of CPT-11 (irinotecan hydrochloride) was severe diarrhea, which is caused by symbiotic bacterial β-glucuronidase, and that of CPT-11 could be reduced by bacterial β-glucuronidase inhibitors. **In 2011**, Zwielehner et al. [12] reported that CC patients had lower bacterial loads than healthy controls. Chemotherapy can lead to changes in the GM, which is consistent with the occurrence of *Clostridium difficile* infection in some patients. In addition, GM changes may have systemic effects and lead to the development of CC-related mucositis. **In 2012**, Lin et al. [13] showed that irinotecan chemotherapy changed the GM of rats and increased the abundance of potentially pathogenic bacteria, such as *Clostridium cluster XI* and *Enterobacteriaceae*, and that oral glutamine could partially alleviate the toxicity of irinotecan and cause temporary changes in the GM.

In 2013, Iida et al. [14] reported that disruption of the GM impairs the subcutaneous tumor response to platinum-based chemotherapy, and the efficacy of oxaliplatin depends on the ability of the GM to activate myeloid cells and release reactive oxygen species (ROS). GM dysbiosis leads to decreased ROS levels, resulting in a decrease in the efficacy of CC. Viaud et al. [15] reported that cyclophosphamide can cause gram-positive bacteria to translocate to mesenteric lymph nodes and the spleen, thereby stimulating Th1 and Th17 cells to produce immune responses, while other sterile mice treated with antibiotics for gram-positive bacteria fail to produce this response, indicating that CC can cause GM translocation. The use of some antibiotics may disrupt these gram-positive bacteria, reducing their beneficial effects. **In**

Table 6 The historical direct cited papers in GM/CC

Sort	DOI	Document Type	Journals	First Author	Year	LCS	GCS	Top Papers
1	10.4161/cbt.7.12.6940	Animal study	Cancer Biol. Ther	Stringer, AM	2008	34	139	Yes
2	10.1086/599346	Clinical study	Clin. Infect. Dis	van Vliet, MJ	2009	61	206	Yes
3	10.3181/0810-RM-301	Animal study	Exp. Biol. Med	Stringer, AM	2009	43	170	Yes
4	10.1126/science.1191175	Animal study	Science	Wallace, BD	2010	72	728	Yes
5	10.1371/journal.ppat.1000879	Review	PLoS Pathog	van Vliet, MJ	2010	66	307	Yes
6	10.1371/journal.pone.0028654	Clinical study	PLoS One	Zwielehner, J	2011	48	159	Yes
7	10.1371/journal.pone.0039764	Animal study	PLoS One	Lin, XB	2012	44	121	No
8	10.1126/science.1240527	Animal study	Science	Iida, N	2013	170	1584	Yes
9	10.1126/science.1240537	Animal study	Science	Viaud, S	2013	192	1454	Yes
10	10.1111/apt.12878	Review	Aliment. Pharmacol. Ther	Touchefeu, Y	2014	71	314	Yes
11	10.1007/s00248-013–0355-4	Clinical study	Microb. Ecol	Montassier, E	2014	34	115	No
12	10.1111/apt.13302	Clinical study	Aliment. Pharmacol. Ther	Montassier, E	2015	86	324	Yes
13	10.4238/2015.May.25.16	Animal study	Genet. Mol. Res	Gui, QF	2015	32	168	Yes
14	10.1016/j.immuni.2016.09.009	Animal study	Immunity	Daillere, R	2016	81	566	Yes
15	10.1002/cncr.30039	Clinical study	Cancer	Galloway-Pena, JR	2016	40	113	No
16	10.1016/j.cell.2017.07.008	Clinical study	Cell	Yu, TC	2017	95	1303	Yes
17	10.1038/nrc.2017.13	Review	Nat. Rev. Cancer	Roy, S	2017	65	615	Yes
18	10.1038/nrgastro.2017.20	Review	Nat. Rev. Gastroenterol. Hepatol	Alexander, JL	2017	117	596	Yes
19	10.1016/j.biopha.2018.08.165	Animal study	Biomed. Pharmacother	Yuan, L	2018	39	132	No
20	10.1186/S13046-018–0985-Y	Clinical study	J. Exp. Clin. Cancer Res	Zhang, S	2019	32	186	Yes

LGS denotes local citation score in the local downloaded papers; GCS denotes global citation score in the WoSCC database; Top papers represent highly cited papers or reviews

2014, Montassier et al. [16] showed that the alpha diversity of the GM decreased sharply after chemotherapy. During chemotherapy, the abundance of *Firmicutes* and *Actinobacteria* decreased, while that of *Bacteroidetes* and *Proteobacteria* increased. At the genus level, the abundance of *Bacteroidetes* and *Escherichia coli* increased sharply, accompanied by a decrease in the abundance of *Fecalibacterium*, *Rothia*, and *Bifidobacterium*. Chemotherapy-induced changes in the GM may cause serious side effects in immunosuppressive cancer patients. **In 2015**, Gui et al. [17] showed that in mice treated with cisplatin combined with an antibiotic mixture (ABX), the tumor size was greater than that in mice treated with cisplatin alone, and the survival rate was significantly lower. In contrast, the mice treated with cisplatin combined with *Lactobacillus* had smaller tumors, greater survival rates, and enhanced antitumor responses. Probiotic combination therapy can enhance the anti-growth and pro-apoptotic effects of cisplatin. The composition and functional imbalance of the GM community associated with chemotherapy-induced gastrointestinal mucositis were determined.

In 2016, Daillère et al. [18] reported that the anticancer effect of cyclophosphamide depends on intestinal bacteria, among which *Enterococcus hirae* (*E. hirae*) and *Barnesiella intestinihominis* (*B. intestinihominis*) were crucial. The former migrates from the small intestine to secondary lymphoid organs and increases the proportion of CD8 + /Treg cells, while the latter enriches the colon and promotes the infiltration of IFN-γ-producing γδT cells into tumors. Galloway-Peña et al. [19] reported that the baseline fecal alpha diversity of patients with infection during chemotherapy was significantly lower than that of patients without infection. A significant decrease in oral and fecal microbial alpha diversity was observed during chemotherapy. Microbiome analysis can help reduce the incidence of infection complications during chemotherapy. **In 2017**, a study [20] showed that *Fusobacterium nucleatum* (*F. nucleatum*) promoted the chemoresistance of colorectal cancer (CRC) to activate the autophagy pathway by targeting specific innate immune signals and microRNAs. Reducing the specific GM in CRC patients may improve the tumor response to CC and reduce cancer recurrence. **In 2018**, Yuan et al. [21] showed that GM dysbiosis may reduce the therapeutic effect of 5-fluorouracil (5-FU) on subcutaneous colon tumors. ABX administration destroyed the GM and reduced the antitumor efficacy of 5-FU, but supplementation with probiotics did not significantly improve the efficacy of 5-FU. Moreover, 5-FU treatment also reduced the alpha diversity of the GM in the mice. **In 2019**, Zhang et al. [22] showed that high *F. nucleatum* abundance is associated with chemoresistance in patients with advanced CRC who underwent standard 5-FU-based adjuvant chemotherapy, and *F. nucleatum* can promote 5-FU chemoresistance by upregulating BIRC3 expression in CRC.

3.6 High-cited papers in GM/CC research

3.6.1 Top 20 most cited articles in GM/CC research

Highly cited research holds immense significance in the academic and scientific landscape. It serves as a testament to the impact that a particular study has had on its field. Table 7 lists the top 20 highly cited articles (published in 2008–2023), and they were mainly from world-renowned journals, such as *Science* (n = 4), *Cell* (n = 3), *Nature* (n = 1). Such research made a meaningful contribution to the field of GM/CC study.

Firstly, some articles show there is an interaction between CC and GM. On the one hand, some of the abovementioned papers depicted CC-driven GM dysbiosis [12, 23], such as the change in alpha diversity, an increase in pathogenic bacteria [10] and a decrease in beneficial bacteria [12]. On the other hand, some papers mentioned the effect of GM on CC, for example, GM can modulate anticancer effects of chemotherapeutics [14, 15, 17], chemoresistance [20], and CC-induced toxicity such as diarrhea and mucositis [8, 9].

Secondly, several papers showed that specific GM can predict the outcome of CC. For instance, *E. hirae* and *B. intestinihominis* can enhance cyclophosphamide-related immunomodulatory effects [18], while *F. nucleatum* can promote 5-FU chemoresistance [22]. Moreover, a study [24] showed that *Candida albicans* bacteremia in cancer patients was thought to develop from gastrointestinal (GI) colonization and subsequently translocate to the bloodstream after CC. After depletion of the GM and stable GI colonization of *Candida albicans*, cyclophosphamide led to 100% mortality, while selective neutrophil or macrophage depletion, lymphocytopenia or GI mucosal destruction alone did not lead to mortality.

Thirdly, GM may regulate the efficacy and toxicity of CC by affecting metabolism and immune function. In 2017, a study [25] in *Cell* showed that the GM can enhance or inhibit the effect of 5-FU and ribonucleotide metabolism by transforming metabolic drugs involving the bacterial vitamins B6 and B9. A study [26] in *Cell* showed that bacterial metabolism affects the host response to cancer chemotherapeutics. A 2021 study [27] found that GM metabolite butyrate can enhance antitumor therapeutic efficacy by modulating cytotoxic CD8 + T cell immunity. Furthermore, A 2023 study [28] in *Nature* showed that the GM-derived tryptophan metabolite 3-IAA affects the chemotherapeutic efficacy in pancreatic cancer.

Phage-guided nanotechnology can change the GM to modulate the outcome of CC. A 2019 study [29] showed that phage-guided nanotechnology may inspire new ways to treat CRC. Targeted drug delivery targeting *F. nucleatum*-enriched

Table 7 The top 20 cited original research related to the GM/CC

No	DOI	First author	Year	Journals	IF	JCR	TC
1	10.1126/science.1240527	Iida, N	2013	Science	44.7	Q1	1584
2	10.1126/science.1240537	Viaud, S	2013	Science	44.7	Q1	1454
3	10.1016/j.cell.2017.07.008	Yu, TC	2017	Cell	45.5	Q1	1303
4	10.1126/science.1191175	Wallace, BD	2010	Science	44.7	Q1	728
5	10.1016/j.immuni.2016.09.009	Daillere, R	2016	Immunity	25.5	Q1	566
6	10.1111/apt.13302	Montassier, E	2015	Aliment. Pharmacol. Ther	6.6	Q1	324
7	10.1016/j.cmet.2021.03.002	He, Y	2021	Cell Metab	27.7	Q1	303
8	10.1371/journal.ppat.0040035	Koh, AY	2008	PLoS Pathog	5.5	Q1	260
9	10.1038/s41551-019–0423-2	Zheng, DW	2019	Nat. Biomed. Eng	26.8	Q1	254
10	10.1126/science.aax0701	Fluckiger, A	2020	Science	44.7	Q1	240
11	10.1086/599346	van Vliet, MJ	2009	Clin. Infect. Dis	8.2	Q1	206
12	10.1186/s13046-018–0985-y	Zhang, S	2019	J. Exp. Clin. Cancer Res	11.4	Q1	186
13	10.3181/0810-RM-301	Stringer, AM	2009	Exp. Biol. Med	2.8	Q2	170
14	10.1016/j.cell.2017.03.040	Scott, TA	2017	Cell	45.5	Q1	168
15	10.4238/2015.May.25.16	Gui, QF	2015	Genet. Mol. Res	0.6	Q4	168
16	10.1016/j.cell.2017.03.046	Garcia-Gonzalez, AP	2017	Cell	45.5	Q1	166
17	10.1126/sciadv.aba1590	Dong, X	2020	Sci. Adv	11.7	Q1	164
18	10.1371/journal.pone.0028654	Zwielehner, J	2011	PLoS One	2.9	Q1	159
19	10.4161/cbt.7.12.6940	Stringer, AM	2008	Cancer Biol. Ther	4.4	Q2	139
20	10.1038/s41586-023–05728-y	Tintelnot, J	2023	Nature	50.5	Q1	137

tumor tissue can be achieved through phage guidance, thereby enhancing the efficacy of CC drugs and reducing drug damage to normal tissue, and phage-specific removal of *F. nucleatum* can reduce the resistance of CRC to chemotherapeutic drugs. A 2020 study [30] showed that enterococcal bacteriophages can enhance the efficacy of cyclophosphamide antitumor therapy. Moreover, dietary fiber protects against CRC in a microbiota- and butyrate-dependent manner [31]. Specific measures such as bacterial β-glucuronidase inhibitors can also reduce the toxicity of CC [11].

3.6.2 Top 10 most cited reviews in GM/CC research

The reviews can help researchers understand new progress, current problems and future trends in this field and provide timely guidance. Table 8 shows the top 10 most cited reviews. Several review articles [2, 32–34] have overviewed the role of GM in cancer and mechanisms by which GM influence cancer growth, outlined the impact of the GM on oncological pathogenesis, immune responses and treatment efficacy and toxicity, demonstrated various approaches in modulation methods of GM, and discussed current limitations, ongoing efforts, and future perspectives in cancer treatment. Two review articles [35, 36] mentioned the role of the GM in the pathogenesis of chemotherapy-induced mucositis, including the modification of intestinal barrier function and repair mechanisms and host innate immunity. There is crosstalk between the GM and immune cells. Two papers [37, 38] outlined the links between the GM and immune development and function and between the GM and anticancer immunosurveillance. A 2020 paper [39] in *Nature* revealed that the GM was associated with human immune cell dynamics, and changes in the concentrations of different types of immune cells in the blood may be directly related to the presence of different GMs. Furthermore, A 2018 review [40] proposed the concept of pharmacomicrobiomics and outlined the mechanisms of anticancer drug-microbiota interactions.

3.7 High-frequency keywords in GM/CC research

To identify hotspots in GM/CC studies, we examined important index keywords. In this study, a total of 4,294 keywords were extracted, including 1,951 authors' keywords and 2,343 keywords plus.

Figure 5A and Fig. 5C show the top 50 authors' keywords and keywords plus. Among the authors' keywords, the common terms were "chemotherapy", "gut microbiota", "colorectal cancer", "probiotics", "inflammation", "mucositis", "breast cancer", etc. Among the keywords plus, the top-ranked terms were "gut microbiota", "chemotherapy", "colorectal-cancer", "*Fusobacterium-nucleatum*", "inflammation", "efficacy", "diversity", "chain fatty acids", "probiotics", "resistance", "mechanisms", etc. The keyword evolution may reflect frontier knowledge. Figure 5B and Fig. 5D depict the trends of the authors' keywords and keywords plus, revealing that metabolomics, intestinal barrier, immune system, regulatory T cells, *F. nucleatum*, and chain fatty acids had attracted increased interest.

In accordance with the co-occurrence keywords and the correlation, a cluster analysis was performed. Each clustered keyword was assigned a category based on the same color. Common keywords (frequency ≥ 10) were divided into four clusters (Fig. 6A).

Cluster 1 (red boxes): This showed that the links between the GM and the efficacy of CC and the mechanism by which the GM affects CC, including tumor microenvironment, immunity (such as regulatory T cells), inflammation

Table 8 The top 10 cited reviews related to the GM/CC

No	DOI	First author	Year	Journals	IF	JCR	TC
1	10.1038/nrc.2017.13	Roy, S	2017	Nat. Rev. Cancer	72.5	Q1	615
2	10.1038/nrgastro.2017.20	Alexander, JL	2017	Nat. Rev. Gastroenterol. Hepatol	45.9	Q1	596
3	10.1038/s41571-018–0006-2	Routy, B	2018	Nat. Rev. Clin. Oncol	81.1	Q1	361
4	10.3390/cancers11010038	Vivarelli, S	2019	Cancers	4.5	Q1	342
5	10.1111/apt.12878	Touchefeu, Y	2014	Aliment. Pharmacol. Ther	6.6	Q1	314
6	10.1371/journal.ppat.1000879	van Vliet, MJ	2010	PLoS Pathog	5.5	Q1	307
7	10.1038/s41586-020–2971-8	Schluter, J	2020	Nature	50.5	Q1	281
8	10.1136/gutjnl-2020–321153	Cheng, WY	2020	Gut	23	Q1	193
9	10.1186/s40168-018–0483-7	Panebianco, C	2018	Microbiome	13.8	Q1	192
10	10.1016/j.phrs.2012.09.002	Bengmark, S	2013	Pharmacol. Res	9.1	Q1	155

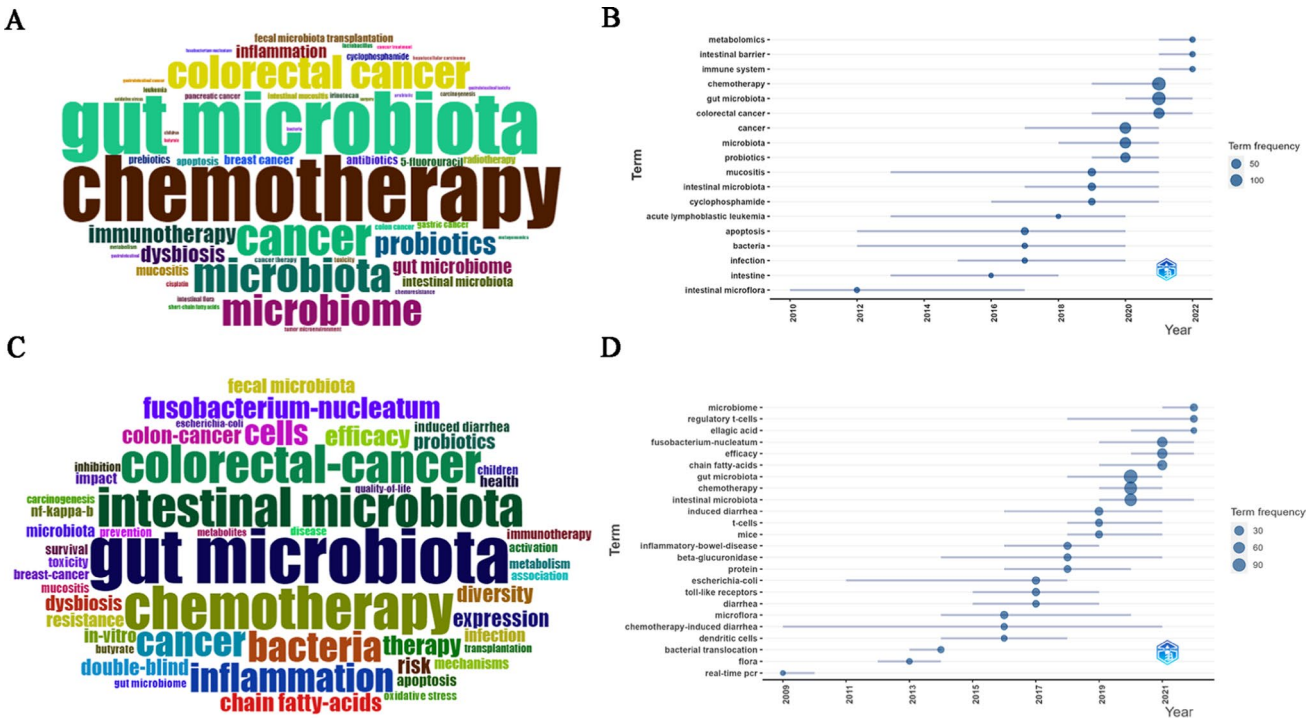

Fig 5. **A** Top 50 Author's keywords in GM/CC research (the size of the font represents the frequency of occurrence). **B** Trend topics of Author's keywords (word minimum frequency set to 5, number of words per year set to 3) in GM/CC research (the abscissa represents the year, and the ordinate represents the hot keywords of this year). **C** Top 50 Keywords Plus in GM/CC research. **D** Trend topics of Keywords Plus (word minimum frequency set to 5, number of words per year set to 3) in GM/CC research (the abscissa represents the year, and the ordinate represents the hot keywords of that year)

(such as nf-kappa-b), metabolism (such as short-chain fatty acids), apoptosis, oxidative stress, DNA-damage, pathway and protein.

Cluster 2 (green boxes): This showed that links between the GM and CC-induced toxicity (such as gastrointestinal toxicity, intestinal mucositis, gastrointestinal mucositis, diarrhea, induced diarrhea, 5-fluorouracil, capecitabine, oxaliplatin, paclitaxel and irinotecan) and the mechanisms of CC-induced toxicity (such as β-glucuronidase, toll-like receptors, pharmacokinetics and gene-expression).

Cluster 3 (blue boxes): This showed that the impact of specific bacteria (such as *Fusobacterium nucleatum* and *Helicobacter pylori*), tumor microbiome, and GM-derived metabolites (such as chain fatty-acids, short-chain fatty acids and butyrate) on carcinogenesis and cancer therapy (such as gastric cancer, colorectal cancer, pancreatic cancer, antitumor immunity and immunotherapy).

Cluster 4 (yellow boxes): This showed that the modulation methods of GM in improving cancer therapy, such as prebiotics, probiotics, synbiotics, antibiotics, and fecal microbiota transplantation.

We further used VOSviewer to analyze the trends of keywords. As shown in Fig. 6B, yellow nodes were centered around Clusters 1 and 3, and the keywords trend were expressed by the keyword "concentrated year" and "occurring" (year, time), including "efficacy" (2021, 67), "mechanisms" (2020, 33), "metabolites" (2021, 10), "short-chain fatty acids" (2021, 11), "tumor microenvironment" (2021, 15), "intestinal barrier" (2021, 15), "*Fusobacterium nucleatum*" (2021, 10), "tumor microbiome" (2022, 17), "pancreatic cancer" (2021, 19), "gastric cancer" (2021, 16), and "breast cancer" (2021, 30).

4 Discussion

4.1 Characteristics of publications

From 2004 to 2023, GM/CC research progressed through elementary stages (2004–2012), a slow development phase (2013–2018), rapid development (2018–2021), and steady development (2021–2023). The National Institutes of Health

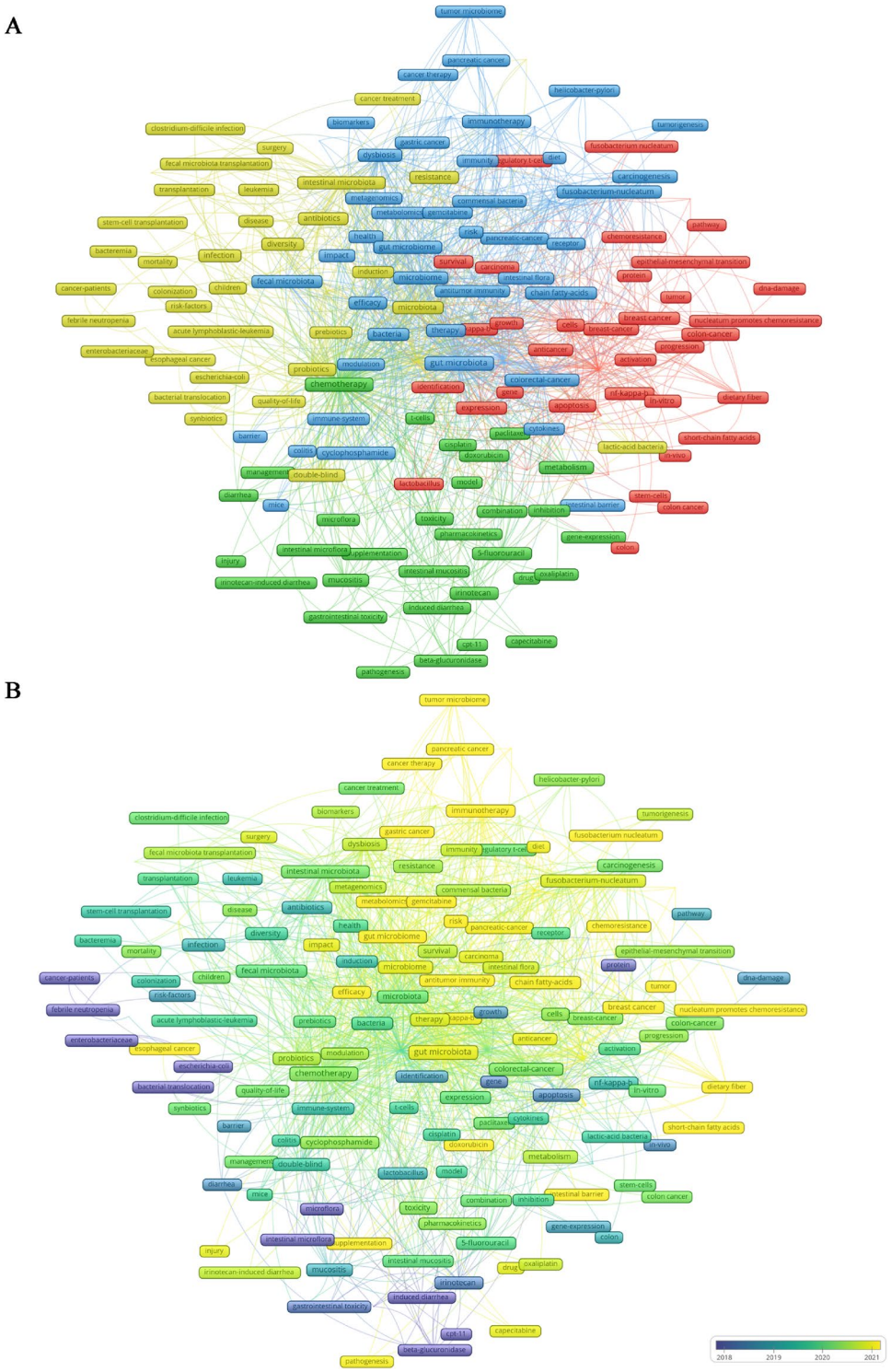

Fig 6. **A** Cluster analysis of common keywords (frequency ≥ 10) in GM/CC (different colors represent different clusters, the size of the circle represents the frequency at which the keywords appear, and the thickness of the line represents the total link strength between keywords). **B** Trends in keywords (frequency ≥ 10) over time based on all keywords of publications in GM/CC (the purple boxes represent the earliest keywords, and the yellow boxes represent the latest keywords, which may represent the research trend in recent years)

in the US launched the Human Microbiome Project in 2007. In 2008, the European Union launched the Human Intestinal Metagenome Project. In 2010, a new direction was opened for studying the human GM gene catalogue [41]. During this period (2004–2012), the research was in the initial stage of exploration, and the Np is small. In 2013, GM/CC research made breakthroughs and two studies [14, 15] published in *Science* found that the GM can influence the efficacy of CC. Correspondingly, GM/CC research began to gain more attention, and the Np began to increase. Subsequently, more and more countries began to pay attention to microbiome research. In 2016, the US initiated the National Microbiome Initiative. In 2017, Chinese Academy of Sciences took the lead in initiating the China Microbiome

Initiative. Hereby, since 2018, GM/CC research had received increasing attention and produced many papers. Notably, the global outbreak and subsequent pandemic of COVID-19 had significantly impacted the work of scientists and publishers, leading to the interruption of some research and delays in publications. Consequently, this may have adversely affected research output and hindered continuous development in the years 2021–2023.

This study showed that *Cancers*, the *International Journal of Molecular Sciences*, and the *Journal of Global Antimicrobial Resistance* published the most papers on GM/CC. The publication output of a journal is directly influenced by both the number of submissions and the acceptance rate. Strategies in these journals to enhance these factors include simplifying the submission process, efficient manuscript handling and shorter review cycles further facilitate increased publication output. Additionally, implementing open access policies enhances the accessibility and visibility of research, potentially boosting the number of submissions. The most highly cited articles were mainly published in *Science*, followed by *Cell*, and *Nature*. These journals are renowned internationally and have high IFs and TCs, indicating that these prestigious journals are more likely to publish high-quality research in the future.

China and the United States were leading the way in GM/CC research may be related to their advanced research facilities, significant investments in research and development, collaborative research efforts, large patient populations for clinical trials, the launch of specialized microbial research programs, growing interest and awareness in the fields. The most productive institutions were mainly from China and France. Inserm, UDICE-French Research Universities and Unicancer from France and Tsinghua University, Chinese Academy of Sciences, Sun Yat-Sen University and Shanghai Jiao Tong University from China are well-known universities or research institutes. These institutions have received strong support from government funds and attracted a large number of outstanding talents due to their strong influence. The most prolific authors were mainly from Gustave Roussy and the University of Minnesota. As highly cited scholars in the world from famous cancer centers and world-class universities, they had received a lot of financial and technical support from countries, governments and institutions. Zitvogel Laurence from Gustave Roussy in France, with the highest Np and H-index, contributed to the study of GM/CC, especially the effect of GM on the anticancer effects of cyclophosphamide [15, 18] and the efficacy of chemotherapy in colon cancer [42] and breast cancer [43], and the action of the probiotic *Enterococcus hirae* [18, 30]. She was also at the core of the authors' collaboration and had close cooperation with Daillere Romain. Rashidi Armin and Weisdorf Daniel J from the University of Minnesota have long been engaged in evaluating the effect of CC on the GM in acute leukemia and the key role of the GM in acute leukemia-associated infection complications [44, 45]. Staley Christopher and Rehman Tauseef also participated in the related research. Bowen Joanne M from the University of Adelaide focused on the role of the GM in CC-induced GI toxicity [46], diarrhea [47] and cognitive impairment [48].

4.2 Current research status and hotspots

Hotspots were found by the analysis of common keywords and highly cited papers in GM/CC research; these hotspots were enriched in four aspects. (1) GM affects the efficacy and toxicity of CC. (2) The GM can serve as a biomarker for estimating the efficacy and toxicity of CC treatment. (3) Potential mechanisms involved in GM modulation of the CC. (4) Modulation of the GM can improve CC outcomes.

4.2.1 The GM affects the efficacy and toxicity of CC

Efficacy is the most critical factor for chemotherapeutics. Most related studies have focused on the effect of the GM on the CC, elaborating on the role of the GM in facilitating and abrogating drug efficacy [2]. Related research shows that the features of the GM are linked to chemotherapy outcomes in cancers such as gastrointestinal cancer [49] and breast cancer [50], and the composition and abundance of the GM differ between chemotherapy responders and nonresponders [51]. On the one hand, the GM and its metabolism can affect the host response to CC [15, 26]. A well-balanced GM can contribute to the anticancer response of CC [17], and its metabolites could also promote the efficacy of CC [27]. However, gut dysbiosis can promote chemotherapy resistance, including gemcitabine/paclitaxel resistance to pancreatic cancer [52], 5-FU resistance to CRC [21] and docetaxel resistance to prostate cancer [53], cisplatin resistance to epithelial ovarian cancer [54]. Moreover, pretreatment for cancer-related dysbiosis (or disease-related and medication-related dysbiosis) and chemotherapy drug-induced dysbiosis can further affect the efficacy of chemotherapy [2]. On the other hand, specific bacteria can affect the host response to CC. For example, *Akkermansia muciniphila* (*A. muciniphila*) may enhance the antitumor effect of cisplatin in lung cancer mice [55]. The abundance of *A. muciniphila* was positively correlated with the antitumor effect of FOLFOX in colon cancer patients [56]. *Enterococcus hirae* compensated for cancer-associated dysbiosis

and facilitated the efficacy of cyclophosphamide [18, 57]. Conversely, Yu et al. [20] reported that *F. nucleatum* activated autophagy to lead to oxaliplatin chemoresistance. Zhang et al. [22] showed that *F. nucleatum* reduced the chemosensitivity of CRC cells to 5-FU and was associated with chemoresistance.

Chemotherapy-induced gastrointestinal toxicity, such as gastrointestinal mucositis and diarrhea, is a key factor affecting the completion rate of chemotherapeutics. Several studies [11, 58] have shown that CPT-11 is converted into active SN-38 by carboxylesterase, and the active SN-38 of CPT-11 is metabolized to the inactive metabolite SN-38 glucuronide (SN-38G) during hepatic glucuronidation and then exported to the intestine, where SN-38G is reconverted to SN-38 by β-glucuronidase secreted by gut bacteria, resulting in severe diarrhea. Related studies [11, 59] have shown that β-glucuronidase produced by the GM can regulate the level of the biologically active form of CPT-11 in the intestinal cavity, thereby affecting the toxicity of CPT-11. Certainly, irinotecan-induced diarrhea may be caused by an increase in β-glucuronidase-producing bacteria, such as *Escherichia coli*, but this increase may also be caused by irinotecan, further exacerbating the drug's toxicity [8, 60]. In addition, GM imbalance can be one of the etiological mechanisms underlying doxorubicin-induced cardiotoxicity [61], cisplatin-induced acute liver injury [62], oxaliplatin-induced mechanical hyperalgesia [63], chemotherapy-induced behavioral side effects [64] and cognitive impairment [48]. Reducing treatment-induced toxicity by regulating the GM may lead to improved therapeutic efficacy via adjuvant therapy. For instance, *Prevotella copri* was associated with carboplatin-induced gut toxicity and targeting *Prevotella copri* maypotentially attenuate carboplatin-induced gut mucositis [65]. *A. muciniphila* can attenuate 5-FU-induced gut mucositis [66]. Moreover, the GM may regulate the toxicity of chemotherapeutic drugs by affecting the microbiome, microbial enzymes and microbial metabolites [67].

4.2.2 GM as a biomarker for outcomes of CC

The GM can serve as a biomarker to predict the efficacy of CC treatment. For example, the alteration in the abundance of *Roseburia faecalis* in patients with gastrointestinal cancer might be a predictor of CC efficacy [49]. Compared with nonresponders, docetaxel responders had an increased proportion of *A. muciniphila* before treatment [50]. Moreover, the GM can predict the response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. Responders were overrepresented in butyrate-producing GM, such as *Roseburia*, *Dorea*, and *Anaerostipes*, whereas non-responders were overrepresented in the *Coriobacteriaceae* and *Fusobacterium*. Ten biomarkers were used for the response-prediction classifier, yielding an area under the curve of 93.57% in the training cohort and 73.53% in the validation cohort [68]. The Shannon and Simpson indices of the GM in ovarian cancer patients revealed statistically significant differences between chemoresistant and chemosensitive individuals, and the random forest model, which included *Angleakisella*, *Arenimonas*, and *Roseburia*, exhibited good prediction accuracy, with an area under the receiver operating characteristic curve of 0.909 [69].

In addition, intestinal bacterial β-glucuronidase may be a predictive biomarker of irinotecan-induced diarrhea severity and may aid in selecting cancer patients for irinotecan treatment [70]. A study [71] showed that patients with bacteremia or bloodstream infection (BSI) after chemotherapy had a decrease in overall diversity and group abundance, and machine learning methods were used to develop a BSI risk index that can predict the incidence of BSI with a sensitivity of 90% and a specificity of 90%. Shi et al. [51] showed that, compared with diarrhea patients after neoadjuvant chemoradiotherapy, patients without diarrhea were richer in *Bifidobacterium*, *Clostridia*, and *Bacteroides*. Stringer et al. [47] showed that CC-induced diarrhea was related to the GM, which was characterized by a decrease in *Lactobacillus*, *Bifidobacterium*, *Bacteroides* and *Enterococcus* and an increase in *Escherichia coli* and *Staphylococcus*. Zhang et al. [72] showed that lung cancer patients with a higher relative abundance of specific bacterial genera, such as *Prevotella*, *Megamonas*, and *Streptococcus,* at baseline were more likely to have gastrointestinal reactions. A significant increase in the abundance of *Prevotella* was observed in carboplatin-treated mice, and the content of *Prevotella* was positively correlated with the severity of carboplatin-induced gut mucositis [65].

4.2.3 Potential mechanisms in GM modulation of CC

The GM may influence the outcomes of CC through the "TIMER" mechanism (translocation, immunomodulation, metabolism, enzyme degradation, and reduction in diversity and ecological variation) [2, 73]. (1) **Translocation**: Cyclophosphamide can cause intestinal villus shortening, focal accumulation of inflammatory cells and mucosal barrier damage, leading to translocation of gram-positive bacteria to the mesenteric lymph nodes and spleen, thereby stimulating immune

cells to produce an immune response [15]. The anticancer effect of cyclophosphamide depended on the GM, in which *E. hirae* translocated from the small intestine to secondary lymphoid organs to increase the intratumoral $CD8^+$/Treg ratio [18]. CC-induced infections may arise primarily from the GM through bacterial translocation [74]. (2) **Immunomodulation**: Gram-positive bacteria can stimulate the generation of a specific subset of Th17 cells and memory Th1 immune responses during cyclophosphamide treatment [15]. The GM can regulate chemotherapy-induced small bowel injury via TLR2 signaling and the drug transporter p-gp [75]. The GM mediates cisplatin hepatotoxicity through enhanced inflammatory reactions and oxidative stress [62]. Moreover, GM impacts local and systemic antitumor immune responses through the use of GM metabolites. (3) **Metabolism**: Gut bacteria convert the active metabolite SN-38G of irinotecan to SN-38, resulting in diarrhea [11, 58]. Anticancer fluoropyrimidine drugs can be metabolized by gut bacteria via conserved pathways found in mammalian hosts [76]. The GM can bolster or suppress the effects of fluoropyrimidines by interconverting metabolic drugs involved in bacterial vitamin B_6, B_9 and ribonucleotide metabolism [25]. Bacterial metabolism can affect the host response to chemotherapy, and 5-FU and FUDR can act through bacterial ribonucleotide metabolism to elicit their cytotoxic effects [26]. (4) **Enzyme degradation**: SN-38G is reconverted to SN-38 by β-glucuronidase secreted by intestinal bacteria, resulting in side effects of intestinal toxicity and severe diarrhea [11, 58]. Targeting gut microbial enzymes, especially β-glucuronidase, can improve chemotherapeutic outcomes [58]. Gut bacterial β-glucuronidase inhibitors ameliorate irinotecan-induced toxicity [11]. Squalene epoxidase drives cancer cell proliferation and promotes intestinal ecological imbalance to accelerate the occurrence of CRC. The inhibition of squalene epoxidase can improve the efficacy of CRC chemotherapy [77]. (5) **Reduction in diversity and ecological variation**: Reduced diversity and shifts in the relative abundance of GM were associated with methotrexate chemotherapy-induced gastrointestinal mucositis [78]. Moreover, the microbial diversity of rats treated with irinotecan decreased significantly, while the abundance of *Fusobacteria* and *Proteobacteria* increased, which may be related to the gastrointestinal toxicity of irinotecan [79]. Notably, some scholars [2, 40] applied the concept of pharmacomicrobiomics to exploit drug-microbiota interactions, particularly focused on the interplay between the GM and the pharmacokinetics or pharmacodynamics of cancer treatment.

4.2.4 GM modulation to improve CC

The GM is a potential target for improving CC outcomes [2, 32]. Modulating the GM to improve CC outcomes involves several aspects. (1) **Dietary adjustments**: Dietary components can affect the efficacy of CC. For instance, dietary serine-GM interactions can enhance chemotherapeutic toxicity without altering drug conversion [80]. Dietary strategies can modulate the GM to enhance the antitumor response of CC [81]. Manipulating the GM with caloric restriction prior to CC can have potential benefits [82]. Dietary restriction can alleviate lethal intestinal toxicity caused by 5-FU by preventing the translocation of opportunistic pathogens [83]. (2) **Probiotics and Prebiotics**: Modifying the GM by administering prebiotics that facilitate the expansion of useful bacteria and reduce pathogenic bacteria is helpful aid in cancer treatment [84]. For example, the oral administration of *Bifidobacterium* can enhance the tumor suppressive effect of irinotecan [85] and attenuate its intestinal and hepatic toxicity [86]. Supplementation of *Lactobacillus reuteri* combined with *Clostridium butyricum* can alleviate cisplatin-induced renal injury [87]. *Bifidobacterium longum SX-1326* can mitigate gastrointestinal toxicity following irinotecan chemotherapy by modulating the P53 signaling pathway and the brain-gut axis [88]. (3) **Fecal microbiota transplantation** (FMT): FMT may reverse antibiotic- and chemotherapy-induced gut dysbiosis [89] and can prevent CC-induced mucosal injury and toxicity [90]. FMT could paradoxically prevent life-threatening bacteremia in CC patients [91]. (4) **Antibiotics**: Antibiotics play a dual role in CC. Several studies [92, 93] have shown that antibiotic use is closely related to worse clinical outcomes in CC patients. However, metronidazole pretreatment reduced the abundance of *Prevotella* and alleviated carboplatin-induced intestinal mucosal injury and inflammation [65].

4.3 Emerging research interests and trends

The analysis of keyword trends reveals several emerging hot topics, including the investigation of "efficacy" and the underlying "mechanisms" of various biological processes. Among these, the study of metabolites such as short-chain fatty acids (SCFAs) and the broader field of metabolomics have gained significant attention. Furthermore, there is a growing interest in tumor microenvironment (TME) and immune system and regulatory T cells, as well as the importance of the intestinal barrier in maintaining health. Additionally, *F. nucleatum* and tumor microbiome have emerged as key areas of focus in understanding disease pathogenesis and potential therapeutic interventions.

4.3.1 Metabolomics, metabolites and SCFAs

GM-derived metabolites serve as crucial links between the GM and cancer treatment [94]. For instance, GM-derived SCFAs affect the efficacy and toxicity of antitumor therapy [95]. SCFAs mainly include acetate, propionate and butyrate. Butyrate may enhance the efficacy of oxaliplatin by regulating CD8 + T-cell activity in the tumor microenvironment [27] and improve irinotecan effect [96]. Furthermore, In recent years, more and more studies have begun to focus on the effects of bacterial metabolites on CC. For example, GM-derived tryptophan metabolite 3-IAA affects the chemotherapeutic efficacy in pancreatic cancer [28]. *A. muciniphila*-derived pentadecanoic acid potentiates the sensitivity of gastric cancer to oxaliplatin through modulation of glycolysis [97]. *Desulfovibrio desulfuricans* and its metabolites impart chemoresistance resistance to CRC [98].

4.3.2 Immune system, regulatory T cells and TME

The influence of the GM on the initiation of innate and adaptive immune responses that are beneficial to the host in the context of effective anticancer therapies has recently been highlighted. A study shows that GM is associated with human immune cell dynamics [39]. T and B cells of the immune system interact with the GM to influence the CC [99]. GM and its metabolites can enhance or suppress anti-tumor immune responses. The role of regulatory T cells in TME is crucial in the formation of immune regulation and tolerance, and the induction of their normal immune regulation function is also regulated by GM. The local microbiome composition influences CC efficacy in colon cancer by modulating tolerogenic versus immunogenic ileal epithelial cell death, which in turn influences follicular helper T-cell priming [42].

4.3.3 Intestinal barrier

Intestinal barrier can prevent systemic or local infection caused by bacterial translocation. Tight junction is a major component of the intestinal barrier and is essential for maintaining barrier integrity. Chemotherapy can destroy the intestinal barrier and cause GM imbalance. For instance, mucosal damage may be required for *Candida albicans* dissemination [24]. GM imbalance causes abnormal expression of transmembrane proteins, which in turn destroys barrier function and increases paracellular permeability, causing the infiltration of pro-inflammatory factors in the intestinal cavity, leading to persistent inflammation and intestinal tissue damage. Butyrate can influence immune system function, preserve the integrity of the gut barrier, and minimize the risk of chemotherapy-induced mucositis, which could be effective as a part of cancer therapy [100].

4.3.4 Tumor microbiota and *F. nucleatum*

Several noted studies [101, 102] have explored the correlation between tumor microbiota and chemotherapy, and found that intratumor bacteria can promote metastatic colonization, and mediate tumor response and tumor resistance to gemcitabine by metabolizing gemcitabine to an inactive form. Notably, GM may modulate tumor microbiota. In addition, some studies showed that intratumoral *F. nucleatum* can alter autophagy to promote chemoresistance against CRC [20] and ESCC [103]. *F. nucleatum* can induce chemoresistance in CRC by inhibiting pyroptosis via the Hippo pathway [104]. By utilizing biomimetic nanovehicles for targeted depletion of intratumoral *F. nucleatum*, a synergistic effect is achieved in combination with PD-L1 blockade against breast cancer [105].

4.4 Key research gaps and opportunities for future investigation

Certainly, there are key some research gaps in GM/CC research. By addressing these research gaps and seizing these opportunities for future investigation, the field of GM/CC can advance significantly, leading to improved treatment outcomes and better quality of life for cancer patients.

The key research gaps in the GM/CC research include: (1) Which specific bacterial species within the GM are most closely associated with positive or negative CC outcomes in different cancer types? This question aims to identify key bacterial biomarkers that could predict treatment response and toxicity. (2) What methods should be applied to further research in the field of GM/CC? Employing high-throughput sequencing technologies to perform metagenomic profiling and metabolomic analyses of the GM can provide a comprehensive view of the microbial communities and their

metabolic activities. (3) What are the mechanisms underlying the crosstalk between specific gut bacteria and CC? Identifying these mechanisms could reveal new targets for therapeutic interventions that enhance drug delivery, metabolism, or elimination. (4) How do specific interventions alter the GM composition and subsequently impact the efficacy and toxicity of CC? Understanding the modulatory effects of these interventions could lead to novel adjuvant therapies that improve patient outcomes.

The opportunities for future investigation in GM/CC research include: (1) Identifying Specific Microbial Species and Their Roles: Specific microbial species play critical roles in modulating the efficacy and toxicity of CC or predicting outcomes of CC. Understanding these species and their interactions with CC could lead to the development of more targeted and effective treatment strategies. (2) Mechanisms of Microbial-Drug Interactions: Further research is required to elucidate the mechanisms underlying the interactions between GM and CC. This includes understanding how microbial metabolites, such as SCFAs, affect drug metabolism, absorption, and efficacy. (3) Cross-Disciplinary Collaboration: Cross-disciplinary collaboration among microbiologists, oncologists, immunologists, and other experts is important in mechanism research. This collaboration can lead to innovative approaches and insights that are not possible when working in isolation. (4) Personalized Microbiota-Based Therapies: Develop personalized microbiota-based therapies can enhance the effectiveness of CC while minimizing adverse effects. Efforts should be made to translate findings from preclinical studies into clinical trials, and ultimately, into routine clinical practice. Some related clinical trials from the International Clinical Trials Registry Platform in manipulating the GM via dietary adjustments (NCT06015087, NCT06376604), probiotics (NCT03642548, ChiCTR2100046237, ChiCTR1800016824), or FMT (NCT06403111, ChiCTR2400087820, ACTRN12624000455561, ACTRN12624001104549) have also gradually increased in recent years.

4.5 Limitations of the article

This paper has several limitations. First, the publications included in the SCIE of WoSCC cannot cover all studies in different languages, so we may have missed out on valuable contributions from researchers working in different linguistic contexts and using different databases. However, it is worth noting that the Web of Science is a highly reputable and widely used database that covers a significant portion of scholarly literature. Despite these considerations, we acknowledge that our results may not fully capture the diversity of research perspectives and methodologies that exist globally. Second, a highly competitive publication environment in a journal might result in lower acceptance rates, thereby impacting the final Np. We analyzed highly cited papers to compensate for this flaw. Third, this study is only an analysis of previous studies. Some recent publications may have a greater impact but may be less cited now. In addition, the evolution of microbial analysis platforms and sequencing technologies may also have an impact on the results of the GM/CC research, but we did not analyze the different microbial analysis platforms and sequencing methods that may be involved in different studies.

5 Conclusion

In conclusion, the number of publications in GM/CC had seen a gradual increase over time, with China and the United States contributing the highest number of papers. Among the publishers, *Cancers* had the largest number of papers. INSERM emerged as a prominent leader. Zitvogel L from France stood out as the most productive author. Four distinct research hotspots were identified, focusing on the GM's role in CC efficacy and toxicity, strategies for targeting the GM to enhance CC outcomes, the mechanisms underlying GM's influence on CC, and the relationships between the GM, carcinogenesis, and cancer therapy. Looking ahead, metabolism, GM-derived metabolites, tumor microenvironment, immunity, intestinal barrier, tumor microbiota, and the bacterium *F. nucleatum* are poised to become the new hotspots and trends in GM/CC research. Notably, by conducting more in-depth research, specific microbial species and their roles may be identified, along with the mechanisms governing microbial-drug interactions. This may lay the groundwork for the development of personalized microbiota-based therapies, offering the potential for tailored treatment plans. In the future, manipulating the GM to enhance the effectiveness of cancer treatments and adverse side effects will become possible. In all, this study preliminarily shows the status of publications on GM/CC studies, provides researchers with a clearer impression of the knowledge map of GM/CC, and provides references for GM/CC research by summarizing current hotspots and future directions. By leveraging these insights, relevant researchers, theorists, and stakeholders can effectively utilize the findings to drive advancements in healthcare and personalized medicine.

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Data availability The datasets used and analyzed in this study are available from the corresponding author on reasonable request. Note: query link: https://webofscience.clarivate.cn/wos/woscc/summary/59b34ff3-5e4e-47db-b39c-5312e31ed302-010e528e0c/times-cited-descending/1.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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