The interactions between traditional Chinese medicine and gut microbiota: Global research status and trends

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Background: There is a crosstalk between traditional Chinese medicine (TCM) and gut microbiota (GM), many articles have studied and discussed the relationship between the two. The purpose of this study is to use bibliometric analysis to explore the research status and development trends of the TCM/GM research, identify and analyze the highly cited papers relating to the TCM/GM.

Methods: A literature search regarding TCM/GM publications from 2004 to 2021 was undertaken on August 13, 2022. The main information (full record and cited references) of publications was extracted from the Science Citation Index Expanded (SCI-E) of Web of Science Core Collection (WoSCC). The Bibliometrix of R package, CiteSpace and VOSviewer were used for bibliometric analysis.

Results: A total of 830 papers were included. The publication years of papers were from 2004 to 2021. China had the most publications and made most contributions to this field. Nanjing University of Chinese Medicine and Beijing University of Chinese Medicine were in the leading productive position in TCM/GM research, Chinese Academy of Chinese Medical Sciences had the highest total citations (TC). Duan Jin-ao from Nanjing University of Chinese Medicine had the largest number of publications, and Tong Xiao-lin from China Academy of Chinese Medical Sciences had the most TC. The Journal of Ethnopharmacology had the most published papers and the most TC. The main themes in TCM/GM included the role of GM in TCM treatment of glucolipid metabolism diseases and lower gastrointestinal diseases; the mechanism of interactions between GM and TCM to treat diseases; the links between TCM/GM and metabolism; and the relationship between GM and oral bioavailability of TCM.

Conclusion: This study gained insight into the research status, hotspots and trends of global TCM/GM research, identified the most cited articles in TCM/GM and analyzed their characteristics, which may inform clinical researchers and practitioners’ future directions.
1 Introduction

Traditional Chinese medicine (TCM), as one of the treatment methods in East Asia for thousands of years, has attracted more and more attention due to its good efficacy and fewer side effects (Feng et al., 2021; Lin et al., 2021; Yang et al., 2022). However, due to the controversial theory of TCM, the complexity in the mechanism of TCM, and the unclarity of effective bioactive components, there are still some doubts and misunderstandings about TCM, resulting in the stagnation of research focusing on the development of TCM (Zheng et al., 2020; Che et al., 2022). Gut microbiota (GM) is involved in various metabolic processes in the human body and plays a major role in host immune response (Wang et al., 2018). GM and its metabolites are of great significance to maintain host health and the pathogenesis, prevention, and treatment of diseases (Clemente et al., 2012; David et al., 2014; Canfora et al., 2015). In recent years, GM has become an important frontier and hot topic to understand the development and progress of diseases. 

With this trend, more and more TCM research began to pay attention to GM and provide rich information for TCM researchers (Li et al., 2009; Xu et al., 2017). GM has become a new way of understanding TCM and can elucidate the profound theory of TCM, which is regarded as the golden key to unlock the mystery of TCM (Chen et al., 2016; Feng et al., 2019; Yue et al., 2019; Lin et al., 2021). The crosstalk between GM and TCM is a crucial discovery in life science and a large number of studies have emerged in the last decade (Xu et al., 2017; Zhang et al., 2020; Li et al., 2021). The interactions between GM and TCM mainly include two aspects (An et al., 2019; Dey, 2019). On the one hand, TCM including single compounds, single herbs and herbal formulations can modulate the GM and its metabolites, and reverse the abnormal GM composition (Zhang et al., 2020). On the other hand, GM also has a very important impact on the biotransformation, bioactivity and bioavailability of TCM, thereby affecting its efficacy and toxicity (Yan et al., 2018; Dey, 2019; Feng et al., 2021).

Bibliometric analysis is a method of statistically evaluating the research status, development trends, and the most influential studies in a specific field. Citation analysis is one of the main methods of bibliometrics, which can evaluate the quality and recognition of papers, and better understand the discipline construction and development of a field. At present, many TCM-related areas have been well studied and explored through bibliometric analysis, such as the analysis of research trends on Artemisinin (Dong et al., 2022), TCM nursing technology for insomnia (Wang et al., 2022), acupuncture research about migraine (He et al., 2022), and traditional Chinese health exercises for improving cognitive function (Li et al., 2021). However, there is currently no English literature published on the quantitative analysis of interactions between GM and TCM. After reviewing the retrieving literature, we found that relevant studies appeared and gradually increased since 2004. Therefore, we selected the published papers from 2004 to 2021 for analysis. This article aims to identify the related papers in TCM/GM in recent years and analyze their characteristics, review the regulatory role of the GM in TCM, looking forward to providing references for further research in TCM/GM.

2 Materials and methods

2.1 Data source and search strategy

Web of Science Core Collection (WoSCC) is an important database for obtaining global academic information with a strict screening mechanism and only includes important academic journals in various disciplines in bibliometrics. SCI-E of WoSCC includes the most authoritative and influential mainstream academic journals in natural science, which is considered the best database and has been used extensively in previous bibliometric studies (Li et al., 2021; Wu et al., 2021; Cheng et al., 2022). Therefore, we choose it as the search source.

All searches were performed on the same day (August 13, 2022) to avoid the significant bias caused by database updates. The papers were retrieved from the SCI-E of WoSCC on August 13, 2022. Using the subject term "advanced search" method, the search terms were TS= "Gut Microflora" and “traditional Chinese medicine” and their synonyms (Table 1). Terms related to GM or TCM that entered into the WoS engine were extracted from the Medical Subject Headings (MeSH) from PubMed. The selection criteria were as follows: (1) The publication years were from 2004 to 2021; (2) The document types were limited to “article” and “review”; (3) The language

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With this trend, more and more TCM research began to pay attention to GM and provide rich information for TCM researchers (Li et al., 2009; Xu et al., 2017). GM has become a new way of understanding TCM and can elucidate the profound theory of TCM, which is regarded as the golden key to unlock the mystery of TCM (Chen et al., 2016; Feng et al., 2019; Yue et al., 2019; Lin et al., 2021). The crosstalk between GM and TCM is a crucial discovery in life science and a large number of studies have emerged in the last decade (Xu et al., 2017; Zhang et al., 2020; Li et al., 2021). The interactions between GM and TCM mainly include two aspects (An et al., 2019; Dey, 2019). On the one hand, TCM including single compounds, single herbs and herbal formulations can modulate the GM and its metabolites, and reverse the abnormal GM composition (Zhang et al., 2020). On the other hand, GM also has a very important impact on the biotransformation, bioactivity and bioavailability of TCM, thereby affecting its efficacy and toxicity (Yan et al., 2018; Dey, 2019; Feng et al., 2021).

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TABLE 1 Search queries and refinement procedure.

| Set | Results | Refinement |
|-----|---------|------------|
| 1   | 1087 Query formulation: Step 1: #1 TI OR AB OR AK = (“Gut Microbi*” OR “Gut Microflora” OR “Gut Flora” OR “Gut Microbial Flora” OR “Gut Microecology” OR “Intestinal Microbi*” OR “Intestinal Microflora” OR “Intestinal Flora” OR “Intestinal Microbial Flora” OR “Intestinal Microecology” OR “Gastrointestinal Microbi*” OR “Gastrointestinal Microflora” OR “Gastrointestinal Flora” OR “Gastrointestinal Microbial Flora” OR “Gastrointestinal Microecology” OR “Fecal Microbi*” OR “Fecal Microflora” OR “Fecal Flora” OR “Fecal Microbial Flora” OR “Fecal Microecology” OR “Faecal Microbi*” OR “Faecal Microflora” OR “Faecal Flora” OR “Faecal Microbial Flora” OR “Faecal Microecology” OR “Enteric Bacteri*” OR “Enteric Flora” OR “Enteric Faecal Bac*” OR “Enterec Bacteri*” OR “Enteric Faecal Bac*”) Step 2: #2 TI OR AB OR AK = (“Chinese medicine” OR “Chinese herb*” OR “Chinese herbal medicine” OR “Chinese medicinal herb*” OR “Chinese herbal drug” OR “traditional Chinese medicine” OR “TCM*” OR “Chinese medicinal plant” OR “Chinese materia medica” OR “Chinese decoction” OR “Chinese formula” OR “Chinese prescription” OR “Chinese patent medicine” OR “Chinese herbal formula” OR “Chinese herbal compound” OR “Chinese herbal prescription” OR “Chinese herbal ingredient” OR “Chinese Herbal Preparation” OR “Herbal medicine” OR “Traditional medicine”) Step 3: #1 AND #2 Indexes =SCI-EXPANDED | |
| 2   | 858 Refined by PUBLICATION YEARS: (2004-2021) | |
| 3   | 854 Refined by LANGUAGES: (ENGLISH) | |
| 4   | 830 Refined by DOCUMENT TYPES: (ARTICLES OR REVIEW ARTICLES) | |

The wildcard “*” was used in place of any number of characters for the most comprehensive search of relevant literature.

3 Results

3.1 Annual publication trends in TCM/GM

Figure 1A shows the number of papers (Np) from 2004 to 2021 in TCM/GM research. The annual growth rate in Np was 29.71%, and the doubling time of the Np appeared in 2018. From 2004 to 2010, the annual Np and total Np (n=27, 3.25%) for this period were very small, the average annual Np was 2.14 and relative annual growth rate was 8.89%, indicating that TCM/GM research was in its infancy. The annual Np and total Np (n=176, 21.2%) in this period increased slowly from 2011 to 2017, the average annual Np was 32.14 and relative annual growth rate was 30.77%. From 2018 to 2021, the annual Np and total Np (n=627, 75.5%) for this period increased rapidly, the average annual Np reached 180.75 and relative annual growth rate was 60.03%.

Figure 1B shows the average citations per article and the average citations per year. In 2004 and 2019, the average citations per article were rather high (but the Np was small), indicating that some papers in these years may have important guiding and pioneering significance. In 2015 and 2018, the average citations per year were rather high, indicating that some papers in these years had significant relevance. From 2004 to 2018, the number of citations per year showed an upward trend. After 2018, the average citations per year showed a downward trend, which is exactly the opposite of the annual Np, which is considered likely to be associated with fewer citations for the latest publications.
3.2 Characteristics of papers in TCM/GM

3.2.1 Main authors

Table 2 lists the top 10 authors and their H-index and TC, of which Duan Jin-ao (n = 24), Jiang Shu (n = 17), Qian Da-wei (n = 16), Shang Er-xin (n = 16), Li, Xiao-bo (n = 15) ranked the top five in the Np. Duan Jin-ao from Nanjing University of Chinese Medicine had the most Np and H-index, and Tong Xiao-lin from China Academy of Chinese Medical Sciences had the most TC, indicating that their papers were of high quality and had a great impact on TCM/GM research. Notably, half of the authors were from Nanjing University of Chinese Medicine. Moreover, there were two authors from South Korea.

Figure 2A shows the annual scientific productivity of the top 20 authors. Most authors had published TCM/GM-related papers since 2014, and most authors’ influential papers were published in 2018 and 2019 (the darkest in the graph). Figure 2B shows the collaborations of the top 20 authors. Among them, the cooperation group with Duan Jin-ao as the core had the most collaborators, and most of the collaborators belong to the same institution (Nanjing University of Chinese Medicine), showing the tendency for cooperation within the institution.

3.2.2 Major countries/regions and institutions

Figure 3A shows the country distribution of papers. The papers were mainly from China (716), accounting for about 86.27% of total output, followed by USA (n = 58), South Korea (n = 44), Japan (n = 26) and Australia (n = 12) (Table 3). More than 800 institutions were involved in this study, and the top 10 most productive institutions were shown in Table 3, of which Nanjing University of Chinese Medicine (n = 63), Beijing University of Chinese Medicine (n = 59), Chinese Academy of Sciences (n = 47), Shanghai University of Traditional Chinese Medicine (n = 46) and China Academy of Chinese Medical Sciences (n = 43) were among the top five. The top 10 institutions all were from China, of which Chinese Academy
of Chinese Medical Sciences had the most TC and Nanjing University of Chinese Medicine had the highest H-index.

Figure 3B depicts the partnership of the top 20 institutions in TCM/GM. Among them, Beijing University of Chinese Medicine and China Academy of Chinese Medical Sciences had the closest partnership. Figure 3C shows the annual scientific productivity of the top 10 institutions. We can see that Beijing University of Chinese Medicine had the most NP in the past two years. Figure 3D depicts the main funding agencies, which mainly were from China, especially the National Natural Science Foundation of China (accounting for 54%), indicating that China has strong support for research in related fields.

3.2.3 Main journals
These papers were published in 241 journals. Table 4 shows the top 10 journals in the NP, of which Journal of Ethnopharmacology had the most NP (n = 82), followed by Frontiers in Pharmacology (n = 62), Evidence-Based Complementary and Alternative Medicine (n = 57) and Biomedicine & Pharmacotherapy (n = 32). The TC can show the importance of the journal, and the H-Index can evaluate the academic influence of journals. In the top 10 most productive journals, the Journal of Ethnopharmacology had the highest TC and H-index, followed by Frontiers in Pharmacology, and the Journal of Pharmaceutical and Biomedical Analysis. Figure 4 summarizes the annual NP and the cumulative NP in the top 10 journals. The cumulative NP in these journals was 376, accounting for about 37.94% of all papers, indicating that their excellent productivity.

3.3 Analysis of cited papers in TCM/GM
3.3.1 Historical cited papers of TCM/GM research
Historical direct citation analysis can quickly identify the most relevant and cited significant papers in the development process of a field, draw a historical direct citation map according to the time series, and then trace the source year by year to analyze the historical development. Figure 5 shows the citation relationship of several classic papers, which appeared from 2009 to 2019. Two indicators, local citation score (LCS) and global
citation score (GCS), were used to examine the research importance of the classic papers. LCS corresponds to the citations of a paper in the downloaded dataset, and GCS represents the times a paper had been cited by all papers in the WoS database (Table 5).

In 2009, a review paper titled “Traditional Chinese Medicine: Balancing the Gut Ecosystem” proposed that TCM plays an important role in restoring the gut ecological balance, and the multi-channel regulation of the human gut ecosystem may be a large part of the efficacy during TCM treatment (Li et al., 2009). In 2011, a review article showed that GM can induce comprehensive metabolism of herbal components and enhance the biological activity of ginsenosides (Wang et al., 2011). In 2013, a study showed that Chinese herbal formula can improve the GM in rats with non-alcoholic fatty liver disease (NAFLD) and return it to normal levels (Yin et al., 2013). In 2014, a clinical study showed that Ephedra sinica can exert an anti-obesity effect by regulating the GM of obese women (Kim et al., 2014). An in vitro study demonstrated that the presence of GM plays an important role in the gastrointestinal metabolism of the water extract of root of Scutellaria baicalensis (Xing et al., 2014). In 2015, an experimental study showed that Red Ginseng and Semen Coicis can improve the structure of GM, promote the growth of probiotics such as Bifidobacterium and Lactobacillus,

### Table 3: The top 10 productive countries/regions and institutions involved in the TCM/GM.

| Rank | Countries | Np | TC  | H-index | Institutions | Np  | TC  | H-index |
|------|-----------|----|-----|---------|--------------|----|-----|---------|
| 1    | China     | 716| 12325| 48      | Nanjing University of Chinese Medicine (China) | 63 | 1178| 19      |
| 2    | USA       | 58 | 2598 | 24      | Beijing University of Chinese Medicine (China) | 59 | 719 | 15      |
| 3    | South Korea| 44 | 886  | 16      | Chinese Academy of Sciences (China) | 47 | 949 | 16      |
| 4    | Japan     | 26 | 503  | 14      | Shanghai University of Traditional Chinese Medicine (China) | 46 | 719 | 16      |
| 5    | Australia | 12 | 234  | 6       | China Academy of Chinese Medical Sciences (China) | 43 | 1259| 17      |
| 6    | Germany   | 7  | 192  | 6       | Guangzhou University of Chinese Medicine (China) | 39 | 581 | 14      |
| 7    | India     | 5  | 83   | 4       | Chengdu University of Traditional Chinese Medicine (China) | 37 | 509 | 11      |
| 8    | UK        | 4  | 111  | 4       | Shanghai Jiao Tong University (China) | 35 | 1099| 17      |
| 9    | Netherlands| 4  | 33   | 3       | China Pharmaceutical University (China) | 32 | 602 | 13      |
| 10   | Poland    | 4  | 112  | 4       | Sun Yat-sen University (China) | 22 | 307 | 11      |
and relieve the symptoms of ulcerative colitis (UC) (Guo et al., 2015). A clinical study showed that structure changes of GM (an increase in beneficial bacteria) induced by Gegen Qinlian Decoction (GQD) were associated with its anti-diabetic effect (Xu et al., 2015), which provided an important reference for TCM microecology research. In 2016, A review article on herb-microbiota interactions showed that TCM can play a role in promoting health and preventing diseases by affecting the structure of GM, and some herbal components can play their therapeutic roles through the GM-mediated biotransformation (Chen et al., 2016). Zhou et al. (2016) found that Ginseng polysaccharides can improve intestinal metabolism and absorption of ginsenosides, reinstate the disturbed GM, and promote the growth of *Lactobacillus* and *Bacteroides*. This study showed that even TCM polysaccharides that cannot be digested by the host can still indirectly promote the therapeutic effect, 

### TABLE 4 The top 10 productive journals in the TCM/GM.

| Rank | Journals                                      | Np | TC   | H-index | IF     | Partition | Countries |
|------|-----------------------------------------------|----|------|---------|--------|-----------|-----------|
| 1    | Journal of Ethnopharmacology                  | 82 | 1499 | 21      | 5.195  | Q2        | Ireland   |
| 2    | Frontiers in Pharmacology                     | 62 | 1101 | 16      | 5.988  | Q1        | Switzerland |
| 3    | Evidence-Based Complementary and Alternative Medicine | 57 | 396  | 11      | 2.650  | Q3        | UK        |
| 4    | Biomedicine & Pharmacotherapy                 | 32 | 383  | 11      | 7.419  | Q1        | France    |
| 5    | Phytomedicine                                 | 20 | 149  | 7       | 6.656  | Q1        | Germany   |
| 6    | Journal of Pharmaceutical and Biomedical Analysis | 19 | 349  | 13      | 3.571  | Q2        | Netherlands |
| 7    | American journal of Chinese medicine          | 15 | 298  | 6       | 6.005  | Q1        | USA       |
| 8    | Pharmacological Research                      | 15 | 523  | 12      | 10.334 | Q1        | UK        |
| 9    | Chinese Medicine                              | 14 | 93   | 6       | 4.546  | Q1        | UK        |
| 10   | Medicine                                      | 14 | 22   | 3       | 1.817  | Q3        | USA       |

**FIGURE 4**

(A) The top 10 journals’ annual publications over time in TCM/GM (the size of the circle represents the number of papers, and the larger the circle, the more the number of papers). (B) The cumulative number of papers of the top 10 journals in TCM/GM.
which endows TCM polysaccharides with new effects. Hussain et al. (2016) showed that Daesiho-tang reduced obesity in high-fat diet (HFD)-fed mice by altering gene expression and modulating GM. In 2017, a review article provided an overview of the molecular mechanisms underlying the interaction between TCM and GM (Xu et al., 2017). The other review article summarized herbal and functional foods for the prevention and treatment of cardiometabolic diseases by modulating GM and exerting prebiotic-like activities (Lyu et al., 2017). A study confirmed that Huangqin Decoction can improve dextran sulphate sodium (DSS)-induced colitis by altering the GM (Yang et al., 2017). An animal study demonstrated that the synergistic effect of metformin and Scutellaria baicalensis in lowering cholesterol levels by fecal excretion of bile acids (Han et al., 2017).

In 2018, an animal experiment showed Huang-Lian-Jie-Du Decoction (HLJDD) could improve hyperglycemia and restore the structure and function of dysregulated GM to a normal state by increasing short-chain fatty acids (SCFAs)-producing bacteria and reducing pathogenic bacteria in type 2 diabetes mellitus (T2DM) rats, which provides new ideas for the study of the mechanism of TCM in the treatment of T2DM (Chen et al., 2018). Gao et al. (2018) found that Qijian Mixture can effectively alleviate T2DM, and this effect was related to the altered characteristics of metabolite profiles and GM. Wei et al. (2018) showed that Xiexin-Tang could significantly improve hyperglycemia, lipid metabolism dysfunction and inflammation in T2DM rats, and some GM were closely related to T2DM-related indicators. Subsequently, a clinical trial (Tong et al., 2018) showed that the TCM compound AMC can reduce the hyperlipidemia in patients with diabetes by changing the structure and diversity of the GM and regulating the probiotics of GM. A further animal experiment (Shen et al., 2018) demonstrated that Ginseng polysaccharides can alleviate DSS-induced colitis and enhance the systemic exposure of Rb1 by enhancing microbial deglycosylation and intestinal epithelial uptake of Rb1. The theory of “eighteen incompatible medicaments” in TCM is the most representative case of herbal-herbal interactions. Gancao and Gansui are one of the incompatible herbal pairs. Yu et al. (2018) showed that the Gancao-Gansui combination did not exacerbate gastrointestinal tissue or functional damage, but caused GM dysbiosis and increased the abundance of some rare genera such as Desulfovibrio and Mycoplasma. In 2019, a study (Wu et al., 2019) revealed the Parabacteroides goldsteinii plays a major role in the anti-obesity effect of polysaccharides isolated from Hirsutella sinensis. The other study (Sun et al., 2019) showed that an insoluble polysaccharide in sclerotia of Poria cocos can ameliorate hyperglycemia, hyperlipidemia and hepatic steatosis in mice by modulating GM. Two reviews (Feng et al., 2019; Yue et al., 2019) summarized the interactions between TCM and GM, including its theory, mechanism, and the future prospects and challenges of GM in TCM.

3.3.2 Top 20 most cited original research articles in TCM/GM

Highly cited papers are one of the most valuable indicators in bibliometric methods, which usually are highly recognized. Table 6 lists the top 20 most cited papers in original research. Some papers have been outlined above, for instance, TCM can improve diabetes and insulin resistance (Xu et al., 2015; Liu et al., 2018; Tong et al., 2018; Wei et al., 2018), obesity (Kim et al., 2014; Wu et al., 2019), colitis (Guo et al., 2015; Yang et al., 2017) by adjusting the GM, here we analyze some other highly cited papers. Highly cited papers mainly focused on the effect of TCM on GM to improve obesity and obesity-related diseases. A 2015
animal study (Chang et al., 2015) found Ganoderma lucidum could reduce obesity in mice by modulating GM, which had the highest TC. It pointed out a new direction for studying the mechanism of TCM, and has important guiding significance for TCM microecology research. Furthermore, oral administration of pomegranate peel extract can alleviate tissue inflammation and hypercholesterolemia in HFD-induced obese mice by modulating GM and promoting the growth of *Bifidobacteria* (Neyrinck et al., 2013). The effect of berberine on preventing obesity and insulin resistance in HFD-fed rats is partially

| No. | Title                                                                 | Document Type | First Author | Journals          | Year | LCS | GCS |
|-----|----------------------------------------------------------------------|---------------|--------------|-------------------|------|-----|-----|
| 1   | Traditional Chinese Medicine: Balancing the Gut Ecosystem            | Review        | Li, HK       | Phytother. Res.   | 2009 | 14  | 42  |
| 2   | Bioactivity Enhancement of Herbal Supplements by Intestinal Microbiota focusing on Ginsenosides | Review        | Wang, HY     | Am. J. Chin. Med. | 2011 | 11  | 82  |
| 3   | Structural changes of gut microbiota in a rat non-alcoholic fatty liver disease model treated with a Chinese herbal formula | Article       | Yin, XC      | Syst. Appl. Microbiol. | 2013 | 12  | 58  |
| 4   | Simulated gastrointestinal tract metabolism and pharmacological activities of water extract of Scutellaria baicalensis roots | Article       | Xing, SH     | J. Ethnopharmacol. | 2014 | 10  | 46  |
| 5   | The anti-obesity effect of Ephedra sinica through modulation of gut microbiota in obese Korean women | Article       | Kim, BS      | J. Ethnopharmacol. | 2014 | 12  | 61  |
| 6   | Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula | Article       | Xu, J        | ISME J.          | 2015 | 52  | 275 |
| 7   | Red Ginseng and Semen Coicis can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis | Article       | Guo, MZ      | J. Ethnopharmacol. | 2015 | 20  | 65  |
| 8   | Dae-si-ho-Tang Is an Effective Herbal Formulation in Attenuation of Obesity in Mice through Alteration of Gene Expression and Modulation of Intestinal Microbiota | Article       | Hussain, A   | PLoS One         | 2016 | 12  | 37  |
| 9   | Gut microbiota-involved mechanisms in enhancing systemic exposure of ginsenosides by coexisting polysaccharides in ginseng decoction | Article       | Zhou, SS     | Sci Rep           | 2016 | 26  | 122 |
| 10  | Could the gut microbiota reconcile the oral bioavailability conundrum of traditional herbs? | Review        | Chen, F       | J. Ethnopharmacol. | 2016 | 22  | 100 |
| 11  | *In vivo* therapeutic effect of combination treatment with metformin and Scutellaria baicalensis on maintaining bile acid homeostasis | Article       | Han, K       | PLoS One         | 2017 | 10  | 27  |
| 12  | Balancing Herbal Medicine and Functional Food for Prevention and Treatment of Cardiometabolic Diseases through Modulating Gut Microbiota | Article       | Lyu, M       | Front. Microbiol. | 2017 | 12  | 100 |
| 13  | Gut microbiota drives the attenuation of dextran sulphate sodium-induced colitis by Huangjin decoction | Article       | Yang, Y      | Oncotarget       | 2017 | 16  | 61  |
| 14  | Understanding the Molecular Mechanisms of the Interplay Between Herbal Medicines and Gut Microbiota | Article       | Xu, J        | Med. Res. Rev.   | 2017 | 48  | 149 |
| 15  | Effects of Qiian mixture on type 2 diabetes assessed by metabolomics, gut microbiota and network pharmacology | Article       | Gao, K       | Pharmacol. Res.  | 2018 | 11  | 54  |
| 16  | Ginseng polysaccharides enhanced ginsenoside Rs1 and microbial metabolites exposure through enhancing intestinal absorption and affecting gut microbial metabolism | Article       | Shen, H      | J. Ethnopharmacol. | 2018 | 10  | 44  |
| 17  | Structural Alteration of Gut Microbiota during the Amelioration of Human Type 2 Diabetes with Hyperlipidemia by Metformin and a Traditional Chinese Herbal Formula: a Multicenter, Randomized, Open Label Clinical Trial | Article       | Tong, XL     | mBio             | 2018 | 32  | 146 |
| 18  | Huang-Lian-Jie-Du-Decoction Ameliorates Hyperglycemia and Insulin Resistant in Association With Gut Microbiota Modulation | Article       | Chen, MY     | Front. Microbiol. | 2018 | 16  | 60  |
| 19  | Xiexin Tang improves the symptom of type 2 diabetic rats by modulation of the gut microbiota | Article       | Wei, XY      | Sci Rep           | 2018 | 30  | 110 |
| 20  | Gansao-Gansui combination impacts gut microbiota diversity and related metabolic functions | Article       | Yu, JG       | J. Ethnopharmacol. | 2018 | 12  | 22  |
| 21  | An insoluble polysaccharide from the sclerotium of Poria cocos improves hyperglycemia, hyperlipidemia and hepatic steatosis in ob/ob mice via modulation of gut microbiota | Article       | Sun, SS      | Chin. J. Nat. Med. | 2019 | 13  | 74  |
| 22  | Gut microbiota modulation with traditional Chinese medicine: A system biology-driven approach | Review       | Yue, SJ      | Pharmacol. Res.   | 2019 | 11  | 28  |
| 23  | Gut microbiota, a new frontier to understand traditional Chinese medicines | Review       | Feng, WW     | Pharmacol. Res.   | 2019 | 32  | 133 |
| 24  | Gut commensal Parabacteroides goldsteinii plays a predominant role in the anti-obesity effects of polysaccharides isolated from Hirutella sinensis | Article       | Wu, TR       | Gut              | 2019 | 26  | 292 |
TABLE 6 The top 20 cited original research articles related to the TCM/GM.

| Rank | Title                                                                 | First author | Year | Journals | IF | TC |
|------|----------------------------------------------------------------------|--------------|------|----------|----|----|
| 1    | Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota | Chang, CJ    | 2015 | Nat. Commun. | 17.694 | 680 |
| 2    | Gut commensal Parabacteroides goldsteinii plays a predominant role in the anti-obesity effects of polysaccharides isolated from Hirsutella sinensis | Wu, TR      | 2019 | Gut      | 31.793 | 292 |
| 3    | Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula | Xu, J       | 2015 | ISME J. | 11.217 | 275 |
| 4    | Polyphenol-rich extract of pomegranate peel alleviates tissue inflammation and hypercholesterolaemia in high-fat diet-induced obese mice: potential implication of the gut microbiota | Neyrinck, AM | 2013 | Br. J. Nutr. | 4.125 | 158 |
| 5    | Structural Alteration of Gut Microbiota during the Amelioration of Human Type 2 Diabetes with Hyperlipidemia by Metformin and a Traditional Chinese Herbal Formula: a Multicenter, Randomized, Open Label Clinical Trial | Tong, XL   | 2018 | mBio    | 7.786 | 146 |
| 6    | Gut microbiota-involved mechanisms in enhancing systemic exposure of ginsenosides by coexisting polysaccharides in ginseng decoction | Zhou, SS    | 2016 | Sci Rep  | 4.996 | 122 |
| 7    | Xiexin Tang improves the symptom of type 2 diabetic rats by modulation of the gut microbiota | Wei, XY    | 2018 | Sci Rep  | 4.996 | 110 |
| 8    | Prebiotic Effect of Fructooligosaccharides from Morinda officinalis on Alzheimer’s Disease in Rodent Models by Targeting the Microbiota-Gut-Brain Axis | Chen, DL   | 2017 | Front. Aging Neurosci. | 5.702 | 96 |
| 9    | Phytonutrient diet supplementation promotes beneficial Clostridia species and intestinal mucin secretion resulting in protection against enteric infection | Wlodarska, M | 2015 | Sci Rep  | 4.996 | 86 |
| 10   | The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial | Lee, SJ   | 2014 | Clin. Nutr. | 7.643 | 83 |
| 11   | Structural Changes of Gut Microbiota during Berberine-Mediated Prevention of Obesity and Insulin Resistance in High-Fat Diet-Fed Rats | Zhang, X  | 2012 | PLoS One | 3.752 | 80 |
| 12   | An insoluble polysaccharide from the sclerotium of Portia cocos improves hyperglycemia, hyperlipidemia and hepatic steatosis in ob/ob mice via modulation of gut microbiota | Sun, SS  | 2019 | Chin. J. Nat. Med. | 3.887 | 74 |
| 13   | Role of human gut microbiota metabolism in the anti-inflammatory effect of traditionally used ellagitannin-rich plant materials | Piwowarski, JP | 2014 | J. Ethnopharmacol. | 5.195 | 68 |
| 14   | Red Ginseng and Semen Cocos can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis | Guo, MZ  | 2015 | J. Ethnopharmacol. | 5.195 | 65 |
| 15   | Colon cancer chemopreventive effects of baicalain, an active enteric microbiome metabolite from baicalin | Wang, CZ | 2015 | Int. J. Oncol. | 5.884 | 63 |
| 16   | Metabolism of Rutin and Poncirin by Human Intestinal Microbiota and Cloning of Their Metabolizing alpha-L-Rhamnosidase from Bifidobacterium dentium | Bang, SH  | 2015 | J. Microbiol. Biotechnol. | 3.277 | 63 |
| 17   | Gut microbiota drives the attenuation of dextran sulphate sodium-induced colitis by Huangqin decoction | Yang, Y   | 2017 | Oncotarget | — | 61 |
| 18   | The anti-obesity effect of Ephedra sinica through modulation of gut microbiota in obese Korean women | Kim, BS  | 2014 | J. Ethnopharmacol. | 5.195 | 61 |
| 19   | Mushroom polysaccharides from Ganoderma lucidum and Poria cocos reveal prebiotic functions | Khan, I  | 2018 | J. Funct. Food. | 5.223 | 59 |
| 20   | Berberine Modulates Gut Microbiota and Reduces Insulin Resistance via the TLR4 Signaling Pathway | Liu, D   | 2018 | Exp. Clin. Endocrinol. Diabet. | 2.426 | 58 |

mediated by the GM, which may reduce the exogenous antigen load of the host and increase the SCFAs level in the gut (Zhang et al., 2012). An insoluble polysaccharide from the sclerotium of Poria cocos can improve hyperglycemia, hyperlipidemia and hepatic steatosis by regulating GM (Sun et al., 2019). Fructooligosaccharides from Morinda officinalis can exert prebiotic effects on animal models of Alzheimer’s disease by targeting the microbiota-gut-brain axis (Chen et al., 2017). Moreover, probiotics combined with TCM had synergistic modulatory effects on GM, and TCM seems to act as a potential substitute for probiotics. A clinical trial (Lee et al., 2014) showed that co-administration of probiotics with herbal remedies had an effect on the GM in obese patients, resulting in significant reductions in body weight and waist circumference, which was important for the exploration of new prebiotics. Several articles mentioned the relationship between GM and TCM in other aspects. For example, eugenol may enhance the mucosal barrier by increasing the thickness of the inner mucus layer through microbial stimulation, thereby preventing invading pathogens and diseases (Wlodarska et al., 2015). The metabolism of human GM plays an important role in the anti-inflammatory effect of traditional tannin-rich plant materials (Piwowarski et al., 2014). GM can play an important role in chemical prevention of colon cancer in Scutellaria baicalensis (Wang et al., 2015). Mushroom polysaccharides from Ganoderma lucidum and Poria cocos act as prebiotics to
regulate GM composition, thus potentially contributing to the health promotion effect (Khan et al., 2018). Human GM has an impact on the metabolism and transformation of natural products, such as a study showing that intestinal bacteria play an important role in the metabolism and pharmacological effects of rhamnoglycosides (Bang et al., 2015).

3.3.3 Most local cited references and analysis of burst references

Figure 6A shows the references with the most citations. In 2006, a mouse study (Turnbaugh et al., 2006) identified the GM as a contributing factor in the pathophysiology of obesity, which showed that obesity-associated GM had enhanced and transmissible ability to obtain energy from diet, and compared to ‘lean microbiota’, colonization of ‘obese microbiota’ in germ-free mice can result in a significantly greater increase in body fat. A clinical study (Ley et al., 2006) showed that the relative proportion of Bacteroides was reduced in obese people compared to lean people, and that this proportion increased with weight loss on two types of low-calorie diet. In 2010, Caporaso JG et al. (Caporaso et al., 2010) developed QIIME, which allows analysis of high-throughput community sequencing data. A 2012 clinical metagenome study (Qin et al., 2012) of the GM in T2DM suggested that gut microbial markers may help to classify T2DM. In 2015, Chang et al. (2015) verified Ganoderma lucidum could reduce obesity in mice by modulating the composition of GM. Xu et al. (2015) found that GQD could enrich the population of beneficial bacteria, such as Faecalibacterium, which is associated with its anti-diabetic effect. In 2017, a review article (Xu et al., 2017) provided a detailed description of the molecular mechanisms underlying the interactions between TCM and GM.

Figure 6B shows the top 20 references with the most bursts in this study. As shown in Figure 6B, most of the valuable burst references were from Nature and its sub-journals, showing the important inspiration of high-impact journals for TCM/GM research. In 2011, A review article (Han et al., 2011) mentioned that modulating GM may act as an anti-diabetic mechanism of berberine, providing a new explanation for the therapeutic effects of berberine. In 2012, two papers in Nature suggested that patients with T2DM were characterized by the GM dysbiosis, a decrease in the abundance of some commonly butyrate-producing bacteria, and an increase in various opportunistic pathogens (Qin et al., 2012); there are functional interactions between the GM and host metabolism (Tremaroli and Bäckhed, 2012). A review article (Clemente et al., 2012) in Cell detailed the important role of human GM in host health and specified changes of GM associated with disease. In 2013, a study (Everard et al., 2013) showed that the abundance of Akkermansia muciniphila was reduced in obese and T2DM mice, but prebiotic feeding normalized its abundance, which was associated with an improved metabolic profile. Two reviews (Shen et al., 2013; Zhao, 2013)explored the interrelationships between the GM, obesity and insulin resistance. In 2014, an article (Shin et al., 2014) showed that metformin treatment can increase Akkermansia, which may be associated with improved glucose homeostasis in diet-induced obese mice. Diet can rapidly and reproducibly alter the GM (David et al., 2014). In 2015, a study (Canfora et al., 2015) showed that GM metabolites SCFAs played an important role in control of body weight and insulin sensitivity. An experimental study (Feng et al., 2015) revealed that the GM can convert berberine into a form that can be absorbed by the gut. In 2018, a clinical study in Science suggested that dietary fiber can selectively boost GM to alleviate T2DM. It can be seen that most of the papers come from the research on GM in modern medicine, especially the correlation study between GM and obesity, indicating that modern medicine has important enlightening significance for TCM research.
3.4 Analysis of keywords in TCM/GM

3.4.1 High-frequency keywords and burst keywords

A total of 4049 keywords (1951 author’s keywords and 2118 keywords plus) were extracted from the imported papers. Figure 7A depicts the author’s keywords and keywords plus with the top 50 frequencies. Among author’s keywords, the most used keywords (exclude search terms) were “inflammation”, “ulcerative colitis”, “obesity”, “berberine”, “insulin resistance”, “type 2 diabetes”, “inflammatory bowel disease”, “irritable bowel syndrome”, “non-alcoholic fatty liver disease”, “metabolomics”, “metabolism”, “metabolites”, “pharmacokinetics”, “short-chain fatty acids”, “oxidative stress”, etc. Among keywords plus, the most used keywords (exclude search terms) were “inflammation”, “metabolism”, “expression”, “health”, “oxidative stress”, “obesity”, “chain fatty-acids”, “mechanisms”, “insulin-resistance”, “inflammatory bowel disease”, “antioxidant”, “flavonoids”, etc.

Through keywords with the most bursts detection, we can understand the development and changes of research hotspots, trends, and frontier dynamics within a certain period of time. A total of 20 burst keywords in this study were obtained, as shown in Figure 7B. The result showed that in the early days (before 2016), the effect of GM on the metabolism and biotransformation of TCM ingredients especially panax ginseng compounds K (one of the metabolites of ginsengoside) and flavonoids was the main focus. In the past few years (after 2016), the research focus was mainly on the effects of TCM on the GM of HFD-induced animal models, and the mechanism and clinical research of regulating GM imbalance to prevent and treat HFD-induced glycolipid metabolism diseases and inflammatory bowel disease (IBD). TCM/GM research had...
gone through the stage from pharmaceutical research to preclinical research, and finally to clinical research.

3.4.2 Cluster and trends analysis of high-frequency keywords

Based on the frequency of two or more keywords appearing at the same time, clustering analysis is carried out. This study treated each clustered keyword as a category, then merged it into the cluster with the highest similarity, finally classified all individuals into a category base on same color. Figure 7C shows the clustering results in TCM/GM, which can be divided into three categories.

Cluster 1 (blue topic)

This category was mainly about the interactions between TCM and GM plays an important role in glycolipid metabolic diseases and explains the mechanism of interplay. (Keywords: inflammation, obesity, berberine, mechanisms, insulin-resistance, diet-induced obesity, high fat diet, fatty liver disease, type 2 diabetes mellitus, metabolic syndrome, polysaccharide).

Cluster 2 (red topic)

This category was mainly about the relationship between GM, TCM and lower gastrointestinal diseases. (Keywords: fecal microbiota, herbal medicine, probiotics, inflammatory-bowel-disease, ulcerative-colitis, irritable-bowel-syndrome, efficacy, association, mechanisms, short-chain fatty acids, pathogenesis, expression, health, disease, bile-acids, barrier function).

Cluster 3 (green theme)

This category is mainly related to metabolism of TCM and GM-mediated metabolite, as well as GM-mediated pharmacokinetics and biotransformation of TCM. (Keywords: oxidative stress, antioxidant, identification, flavonoids, pharmacokinetics, biotransformation, liquid chromatography, mass spectrometry, panax ginseng, apoptosis).

Overlaid visual maps, similar to concurrency graphs, are an effective way to predict future trends and hotspots. VOSviewer uses different colors for each keyword in the images based on the average time they appear in all included publications, as shown in Figure 7D, where the blue circles represent the earliest keywords and the yellow circles represent keywords appear in recent years. From 2016 to 2020, there are relatively unbalanced development dynamics in three clusters, more yellow nodes are in the cluster 1 and 2. This showed that clinical research has become a research hotspot in recent years.

4 Discussion

TCM has been widely used worldwide as a complementary alternative therapy because of its clinical efficacy and reduced side effects for thousands of years, but the mechanisms by which TCM prevents and treats disease remains unclear (Xu et al., 2017). In recent years, with the rapid development of high-throughput sequencing, 16S rRNA detection technology and bioinformatics methodology (Caporaso et al., 2010; Qin et al., 2012), people have gradually realized that GM plays an important role in the TCM treatment of disease (Lin et al., 2019; Zheng et al., 2020). Along with this, how TCM regulates the GM to achieve the effect of curing diseases has also become a hot topic that needs to be solved. To better understand the interactions between GM and TCM, we reviewed and analyzed related research papers and summarized the influence of GM on TCM by means of bibliometric methods, and discussed the mechanism of the interactions between the GM and TCM, and provides information for the development, utilization and modernization of TCM.

4.1 Current status and characteristics of literature

The number of publications in TCM/GM can reflect the development stage it had experienced. From the annual Np, 2004-2010 belonged to the initial stage of TCM/GM research. During this period, the GM research had just started, such as the official launch of the Human Microbiome Project and the China-France human intestinal metagenome research cooperation program in 2007. 2011-2017 was in a steady and slow development stage, which showed a consistent trend with the development of GM research (Yuan et al., 2021). And 2018 to present was in a stage of rapid development, which may be due to the rapid development of GM research and modernization of TCM, as well as the increasing interest of researchers in TCM/GM.

The study showed that the papers related to TCM/GM mainly came from China, followed by the US, South Korea and Japan. The top 10 institutions were all located in China, demonstrating good scientific research capabilities of China in TCM/GM. China had the most publications and was at the core of global cooperation, which can be related to long application history of TCM and the high attention and financial support of the government and community of China on the GM program such as funding and technical support of the National Natural Science Foundation and the Chinese Academy of Sciences Microbiome Program initiated in 2017. Nanjing University of Chinese Medicine and Beijing University of Chinese Medicine, as the top Chinese medicine universities in China, had published the most articles. Moreover, Nanjing University of Chinese Medicine published the most papers and had the highest H-index and most high-yield authors, showing its outstanding contribution to TCM/GM research.

The most productive author was Duan Jin-ao, who had contributed to the field of TCM/GM and was a leading pioneer.
in the study of the relationship between GM and TCM, especially the research of TCM metabolomics (Xiao et al., 2020; Zhang et al., 2021) and "eighteen incompatible medicaments" (Yu et al., 2018; Yu et al., 2019), and was at the core of the collaborative relationship between authors. Li Xiaobo from Shanghai Jiao Tong University mainly focused on the GM of spleen deficiency syndrome and the intervention mechanism of Sijunzi decoction (Peng et al., 2020; Ma et al., 2021). Kim, Hojun from Dongguk University was mainly engaged in the research of TCM to improve obesity and metabolic syndrome by regulating GM (Kim et al., 2014; Hussain et al., 2016), while Kim, Dong-hyun from Kyung Hee University was busy studying the role of TCM metabolites in the treatment of diseases such as colitis (Kim et al., 2008; Jang et al., 2019). In terms of the impact of papers, Tong Xiao-lin from China Academy of Chinese Medical Sciences had the highest TC, who has long been engaged in clinical and scientific research on diabetes and its complications. Tong Xiao-lin published many highly cited papers (Xu et al., 2015; Tong et al., 2018) on diabetes, GM and TCM, his papers mainly focused on TCM/GM clinical research. Hsin-Chih Lai from Chang Gung University in Taiwan also had published many highly cited and influential papers (Chang et al., 2015; Wu et al., 2019) as the corresponding author. His papers mainly explored the relationship between GM and TCM such as Ganoderma lucidum and Hirsutella sinensis from the perspective of causality by fecal microbiota transplantation and antibiotic treatment rather than association in ordinary research, which has important inspiration for future research.

The study showed that the Journal of Ethnopharmacology had the most Np, the highest TC and H-index, which mainly focuses on the biological activities of plant and animal medicines used in traditional medicine in the past and present, aiming to promote the development of ethnopharmacology and is a representative journal in the field of complementary medicine. Moreover, Frontiers in Pharmacology, Evidence-Based Complementary and Alternative Medicine, and Biomedicine & Pharmacotherapy also were relatively productive, Pharmacological Research had the highest IF. These journals are internationally renowned and have greater international influence in TCM research, which can provide a reference for the publication of articles in related fields. Meanwhile, we can also see that although most TCM/CM articles were published in China, there was a lack of influential international journals, and it is necessary to improve the international influence of Chinese journals.

### 4.2 Research hotspots and trends

High-frequency keywords are often used to identify hot topics of a field, while cluster analysis is mainly used to find the distribution of main research contents under the research topics. High-frequency keywords co-occurrence and cluster analysis results showed the hotspots and main research contents in TCM/GM, mainly related to the role of GM in TCM treatment of glucolipid metabolic disease and lower gastrointestinal diseases, the mechanism of interactions between GM and TCM to treat diseases, the links between TCM/GM and metabolism, and the relation between GM and the oral bioavailability of TCM.

#### 4.2.1 The role of GM in the TCM treatment of diseases

Metabolic diseases such as obesity, T_{2}DM and hyperlipidemia are associated with GM dysfunction. TCM such as berberine has shown considerable efficacy in the treatment of metabolic disorders by modulating GM (Yang et al., 2021; Zhang et al., 2021). (1) Obesity and Lipid Metabolism: Human GM associated with obesity has been studied earlier (Ley et al., 2006; Tremaroli and Bäckhed, 2012; Zhao, 2013; Shin et al., 2014). Some studies showed that TCM such as Celastrol (Hua et al., 2021), Ganoderma lucidum (Chang et al., 2015) and Daesiho-Tang (Hussain et al., 2016) can attenuate HFD-induced obesity by remodeling GM to inhibit lipid absorption. Moreover, Liu et al. (2019) showed that Coix seed can be used as a prebiotic preparation to reduce body weight and prevent obesity-related metabolic disorders. Wu et al. (2021) found that Bupleurum radix extract can improve the impaired lipid metabolism in HFD-induced obese mice through regulation of GM-mediated FGF21 signaling pathway. Er-Chen Decoction has a beneficial effect on obesity, especially lipid metabolism disorder, which is related to the regulation of GM (Zhao et al., 2021). A meta-analysis showed that oral TCM preparations could improve lipid metabolism disorders in patients by regulating GM (Gong et al., 2022). (2) T_{2}DM and Insulin Resistance: Many herbal monomers and formulations can pass the “bacteria-mucosal immunity-inflammation-diabetes” axis to improve glucose metabolism and treat diabetes (Gao et al., 2017; Zheng et al., 2020). Cao et al. (2019) found that Jingqi-Jiageng Tablet may improve the insulin sensitivity of T_{2}DM mice by improving the GM and promoting the production of SCFAs. Zheng et al. (2020) showed that Bu-Zang-Tong-Luo Decoction has a beneficial effect on diabetic hindlimb ischemia by remodeling the structure of GM. Wang et al. (2019) reported that Ophiopogon japonicus tuber polysaccharide can be used as a new type of functional food to prevent diabetes-related GM dysbiosis and metabolic disorder. Berberine can ameliorate liver injury-induced glucose and lipid metabolism disorders by alleviating ER stress in hepatocytes and regulating GM (Yang et al., 2021). A meta-analysis showed that TCM could regulate GM and improve glucose metabolism in T_{2}DM patients (Zheng et al., 2021). (3) NAFLD: GM is an important target for the TCM treatment of NAFLD (Ma et al., 2017). For instance, Ginsenosides can improve NAFLD through the comprehensive
regulation of GM, inflammation and energy homeostasis (Liang et al., 2021). Gypenosides can modulate GM to attenuate disease progression in mice with NAFLD (Huang et al., 2019). Sheng-Jiang Powder (Li et al., 2020) and GQD (Guo et al., 2018) can alleviate HFD-induced steatohepatitis and improve NAFLD by regulating GM. A review detailed the significance of GM in the pathogenesis of NAFLD and the current status of TCM treatment of NAFLD by regulating GM (Li and Hu, 2020).

Lower gastrointestinal diseases are also a hotspot in TCM/GM research, TCM can regulate GM to treat IBD (mainly UC), irritable bowel syndrome (IBS) and Colorectal cancer (CRC) (1). UC: GM dysbiosis is closely related to UC, and TCM can alter the composition of GM to treat UC by enriching beneficial bacteria or SCFA-producing bacteria and reducing pathogenic bacteria (Feng et al., 2022). For example, Rhubarb Peony Decoction can restore Th17/Treg balance by regulating GM to improve UC (Luo et al., 2019). Li-Zhong Decoction can improve the composition of GM and restore the balance of GM, such as increasing anti-inflammatory factors (Li et al., 2021); (2) IBS: Li et al. (2018) showed that Tong-Xie-Yao-Fang and Fructooligosaccharides from Morinda of Vaccinium vitis-idaea can alter the GM by increasing SCFAs-producing bacteria and reducing pathogenic bacteria (Feng et al., 2022). For example, Eugenol may enhance the anti-inflammatory function of berberine and luteolin (Cao et al., 2020). Furthermore, the metabolism of GM can alter the GM by increasing the level of SCFAs, regulating bile acid (BA) metabolism, and help reduce diet-induced inflammation caused by GM dysbiosis. For instance, the bacterial metabolite butyrate have potential anti-oxidant properties, and as mentioned above, TCM can promote their increase. In addition, probiotics can reduce the level of intestinal oxidative stress through their own antioxidant enzymes and anti-oxidant metabolites, and some TCM such as mushroom polysaccharides from Ganoderma lucidum and Poria cocos (Khan et al., 2018), Fructooligosaccharides from Morinda officinalis (Chen et al., 2017) and Astragalus polysaccharides (Li et al., 2009) have probiotic-like effects and can play this function. (3) Protecting the intestinal barrier: The intestinal mucosal barrier (IMB) is the first line of defense against the invasion of commensal bacteria and pathogenic microorganisms. Under the influence of HFD, inflammatory stimulation, oxidative stress and other factors, the structure and function of IMB may be damaged, which may lead to intestinal injury (leaky-gut). Defects in IMB function are important factors leading to the development of diseases such as IBD. Some TCM can improve the IMB function by adjusting GM (Cao et al., 2019). For instance, Eugenol may enhance the IMB by increasing the thickness of the inner mucus layer through microbial stimulation, thereby preventing invading pathogens and diseases (Wlodarska et al., 2015). Scutellaria-Coptis (Zhang et al., 2020), Ginsenosides (Liang et al., 2021) and GQD (Li et al., 2020) can alleviate IMB damage by inhibiting inflammation and regulating GM.

4.2.3 The connection between TCM/GM and metabolites

TCM/GM-related metabolites are key factors in the curative effect of herbal medicines (Wang et al., 2019). Metabolomic...
analysis is an ideal method to identify changes in TCM/GM-related metabolites (Shen et al., 2018). The interactions of TCM and GM can lead to the increase or decrease of certain metabolites and the production of new metabolites or the disappearance of certain metabolites (Feng et al., 2019). The metabolites mainly include three categories (Feng et al., 2018): (a) metabolites that are transformed from TCM by the GM, such as compound K and baicalin; (b) metabolites that are secreted by the host and modified by GM, such as secondary bile acids; (c) metabolites that are synthesized by GM de novo, such as SCFAs and polysaccharide A.

Herbal compounds can be transformed by the GM (type a metabolites) or metabolized into other types of metabolites in a new scaffold (type c metabolites). On the one hand, GM is involved in the metabolism and biotransformation of TCM components such as flavonoids and ginsenosides by producing specific enzymes, such as reductase and hydrolase (Dey, 2019; Zhang et al., 2020; Xie et al., 2020). TCM-related metabolites mediated by GM can have better bioavailability and bioactivity than their parent compounds. For example, human GM can efficiently metabolize baicalin with minor anti-tumor effect to baicalein with potent anti-tumor effect (Wang et al., 2015). Some metabolites of herbal ingredients influenced by GM were demonstrated to be more cytotoxic to tumor cells than non-metabolites (Kim et al., 2008) and have higher anticomplementary and antimicrobial activity (Xing et al., 2014). The GM can convert berberine to a more easily absorbed but inactive metabolite dihydroberberine through enzymatic catalysis, which is then oxidized back to berberine and incorporated into the blood to exert pharmacological activity (Feng et al., 2015). In fact, under fermentation by the GM, TCM can be metabolized into various metabolites with a wide range of bioactivities to affect its efficacy and toxicity (Pisowarski et al., 2014; Lin et al., 2021). On the other hand, GM-related metabolites influenced by TCM can have a wide range of effects on the therapeutic or side effects of TCM. SCFAs are the major de novo metabolites associated with TCM and the most well-studied in TCM/GM over the past decade (Feng et al., 2018). SCFAs can regulate gut hormone production, gut integrity, energy homeostasis, appetite, and immune function (Canfora et al., 2015). The therapeutic effect of TCM can be partially achieved by affecting SCFAs (Zhang et al., 2012; Zhang et al., 2021). For example, after using Scutellariae radix, Coptidis Rhizoma and their combination, SCFAs-producing bacteria were significantly enriched in T2DM rats, while secondary bile acid-producing bacteria were significantly decreased (Xiao et al., 2020). Xiexin Tang (Wei et al., 2018; Zhang et al., 2021) and HLJDD (Chen et al., 2018) can significantly ameliorate the GM of T2DM rats, increasing the abundance of SCFAs-producing bacteria and promote the production of butyrate (a SCFA fermented by the GM), which may explain their therapeutic efficacy.

### 4.2.4 The relationship between GM and oral bioavailability of TCM

Notably, low oral bioavailability and bioactivity are a perplexing problem for some TCM. GM and its metabolism can directly or indirectly affect the biotransformation of TCM and reconcile the oral bioavailability conundrum of TCM (Chen et al., 2016; Xu et al., 2017; Zhang et al., 2020). This biotransformation may help explain the large interindividual...
variability in responses to TCM, as the composition of GM varies among individuals. Bioavailability is closely related to the blood concentration of TCM, which can directly reflect the efficacy and toxicity of most drugs and is regarded as an important factor in the evaluation of efficacy and safety.

A study (Kim et al., 2008) showed the GM may activate the pharmacological effects of TCM, and is a biocatalytic converter that converts herbal components into bioactive compounds. GM can induce comprehensive metabolism of herbal components and enhance the bioactivity of TCM such as ginsenosides (Wang et al., 2011). TCM is mainly taken orally. After the components of TCM are absorbed into the blood through the gastrointestinal tract, they are mainly metabolized in the liver, and finally generate a variety of metabolites. However, studies have shown that the bioavailability of most compounds in TCM is very low (Zheng et al., 2020). For example, the bioavailability of ginsenosides is typically around 0.1%–0.5% by oral administration (Liu et al., 2009) and the oral bioavailability of berberine is less than 1% (Chen et al., 2011). Flavonoids are key bioactive substances in herbal medicines with pharmacological potential, but their bioavailability is also low (Dey, 2019). Recent studies have shown that TCM ingredients inevitably come into contact with microorganisms in the gastrointestinal tract during oral administration, especially saponins with larger molecular weight, which are usually poorly absorbed in the intestinal tract, have low bioavailability and a relatively long retention time in the intestinal tract. Longer, more susceptible to the influence of GM. Under the action of GM, the components of TCM will undergo a series of structural changes, and the resulting transformation products may have better bioavailability or stronger biological activity than the original components (Kim et al., 2008; Feng et al., 2015; Dey, 2019). Furthermore, the potential of TCM as a therapeutic agent may not only depend on its bioavailability, but its medicinal value may also stem from its positive effects on GM-mediated gastrointestinal health (Lopresti, 2018).

4.3 Related research on specific areas of TCM/GM

Some articles may indicate future research trends, but there may be less chance of being cited. Therefore, we searched for articles and found representative papers among them. The specific studies are as follows:

(1) TCM Syndromes research: GM imbalance is an important part of TCM syndromes characteristic community. For example, GM imbalance and subsequent metabolic changes in patients with qi deficiency affected immunity and energy metabolism, thereby increasing the susceptibility to diseases (Ma et al., 2018). GM in patients with spleen deficiency syndrome (Peng et al., 2020), spleen-yang-deficiency syndrome (Lin et al., 2018), and kidney-yang deficiency syndrome (Chen et al., 2019) had changed, while TCM can help to restore the richness and diversity of GM in specific TCM syndromes (Zheng et al., 2020), which provided insights into the correlation between TCM syndromes and GM imbalance and a new method for further studying the pathogenesis of GM regulating specific TCM syndrome. Two studies have shown that GM can help to distinguish the two TCM syndromes of UC (Zhang et al., 2019) and colorectal cancer (Wang et al., 2020), which can be used as the biological basis for TCM syndrome differentiation and treatment of related diseases. (2) Acupuncture and Moxibustion research: Moxibustion may promote the repair of gastric mucosal injury by increasing the number and types of intestinal beneficial bacteria (He et al., 2019). Acupuncture can effectively alleviate insomnia and change the GM (Huangfu et al., 2019). Acupuncture at specific acupoints can delay the weight loss and tumor development of mice, and change the abundance of specific genera of GM (Xu et al., 2020). Moreover, acupuncture treatment may be an effective method to improve sleep disorders, and the mechanism may be related to the change of GM (Hong et al., 2020). (3) Integrative Chinese and western medicine study: GQD can enhance PD-1 blockade in CRC by remodeling GM (Lv et al., 2019). Berberine has potential benefits in combination with methimazole in modulating GM composition in the treatment of Graves’ disease (Han et al., 2021). In addition, complementary and alternative medicine prevention and treatment strategies such as TCM may help reduce antibiotic use (Raars et al., 2019). Notably, antibiotics disrupt the homeostasis of GM, thereby affecting the efficacy of TCM. Some studies have shown that TCM can reduce its efficacy when combined with antibiotics. For example, Kai-Xin-San can suppress the neuronal inflammation improved the depression-like behavior, while antibiotic treatment attenuated the antidepressant-like effect (Cao et al., 2020). Cassiae Semen had a hepatoprotective effect on NAFLD by modulating GM, and antibiotics can inhibit or eliminate this effect (Luo et al., 2021). Antibiotics can affect the metabolism and pharmacokinetics of the active ingredients of Scutellaria baicalensis, which should not be used in combination with antibiotics in clinical use (Xing et al., 2017). The method of combined application of TCM and western medicine to improve clinical efficacy still needs to be further explored.

4.4 Limitations of the study

This study still has some limitations. First, even though we have found the top cited articles, newly published papers may also have better influence but may be cited less frequently. Second, only the papers included in the SCI-E of WoSCC were searched, and some papers not included in the of WoSCC were not included in the analysis, which may cause some bias in the results. Third, only English literatures-included and the articles/reviews-based search strategy mean that a few articles involving TCM/GM may be ignored. Fourth, this study is only an analysis of research
articles at the current stage. With the rapid development of TCM/GM research, more articles will be available for analysis.

5 Conclusion

In summary, with the help of scientometrics and visual analysis methods, this study preliminarily shows the global research status and trends of interactions between GM and TCM. The results show that in recent years, the research attention of TCM/GM has gradually increased. The TCM/GM research mainly focused on the effects of TCM on the GM of HFD-induced animal models, the mechanism of regulating GM imbalance to prevent and treat glucolipid metabolism diseases and lower gastrointestinal diseases, and the links among GM, metabolism, and oral bioavailability of TCM. In the future, TCM/GM research will delve into more diverse disease types, such as cancers, psychiatric and neurological disorders, and so on. Moreover, more in-depth research will work to identify specific bacteria and metabolites that affect the efficacy and toxicity of TCM, so as to better play the role of TCM treatment. All in all, GM provides a new opportunity for elucidating the mechanism of TCM in treating diseases. TCM can be also a treasure trove of potential prebiotics. GM, especially GM-related metabolites, may be key mediators linking TCM to host physiological states. Increasing explorations of TCM-GM interactions would have the opportunity to revolutionize the way we view TCM. GM-centric research could be the next breakthrough in TCM, and targeting the GM may become a new strategy for treating diseases through TCM in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Author contributions

SY: writing-original draft preparation, manuscript, investigation, and figure preparation. SH: manuscript, investigation, and figure preparation. QW: data collection and manuscript proofreading. YL: conceptualization, methodology, and supervision. LJ: investigation, methodology, and supervision. DC: conceptualization, methodology, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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