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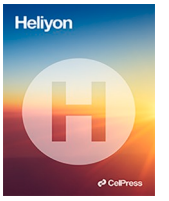

Research article

Comprehensive bibliometric and visualized analysis of research on gut-liver axis published from 1998 to 2022

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ABSTRACT

Background: The concept of the gut-liver axis was proposed by Marshall in 1998, and since then, this hypothesis has been gradually accepted by the academic community. Many publications have been published on the gut-liver axis, making it important to assess the scientific implications of these studies and the trends in this field.
Methods: Publications were retrieved from the Web of Science Core Collection. Microsoft Excel, CiteSpace, VOSviewer, and Scimago Graphica software were used for bibliometric analysis.
Results: A total of 776 publications from the Web of Science core database were included in this study. In the past 25 years, the number of publications on the gut-liver axis has shown an upward trend, particularly in the past 3 years (2020–2022). China had the highest number of publications (267 articles, 34.4%). However, the United States was at the top regarding influence and international cooperation in this field. The University of California San Diego had contributed the most publications. Suk, Ki Tae and Schnabl, Bernd were tied for the first rank in most publications. Thematic hotspots and frontiers were focused on gut microbiota, microbial metabolite, intestinal permeability, bacterial translocation, bile acid, non-alcoholic steatohepatitis, and alcoholic liver disease.
Conclusion: Our study is the first bibliometric analysis of literature using visualization software to present the current research status of the gut-liver axis over the past 25 years. The damage and repair of intestinal barrier function, as well as the disruption of gut microbiota and host metabolism, should be a focus of attention. This study can provide a reference for later researchers to understand the global research trends, hotspots, and frontiers in this field.

1. Introduction

The liver and intestine have a relatively close relationship. In terms of embryonic development, the embryos of the intestine and liver originate from the endoderm, while parts of these organs develop from the foregut [1]. Additionally, the intestine and liver are interconnected through many channels, such as portal blood circulation, hepatic and intestinal lymphatic systems, and bile circulation

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in the biliary system. Marshall postulated the "gut-liver axis" concept in 1998 and expounded that substances, cells, and cytokines between the liver and intestine can regulate and influence each other via the portal vein system [2]. In addition to their anatomical homology, the liver and intestine have been reported to exhibit metabolic interaction and immune correlation [3,4]. Specifically, the liver can communicate with the intestine by releasing primary bile acids and many immune or inflammatory mediators into the bile duct and systemic circulation. In the intestine, metabolites of host and microorganisms (such as secondary bile acids, dietary metabolites, potential pathogenic compounds, etc.) can translocate to the liver through the portal vein and influence liver functions [5].

Common metabolic and infectious liver diseases have been widely spread in the past few decades, which are considered major public health challenges and have caused serious socio-economic burdens [6]. Various liver diseases are characterized by an impaired gut barrier and a disturbed gut-liver axis. Intestinal barrier damage with translocation of immune active mediators has been found in patients with non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and primary sclerosing cholangitis (PSC) [7,8]. In this instance, antigens, metabolites, gut microbiota, and endotoxins in the intestine translocate to the liver through the portal vein, which may exacerbate existing liver diseases through liver inflammation. This is supported by clinical findings that advanced liver disease characterized by cirrhosis and portal hypertension often occurs in conjunction with intestinal barrier damage, and that clinical manifestations can be treated by modulating the gut microbiota [9,10]. The findings of the gut-liver axis have raised hopes for common and rare liver diseases that were previously untreatable. An improved understanding and in-depth study of the gut-liver axis concept will help to re-recognize the treatment approach for liver and intestinal diseases. Many countries have gained remarkable achievements through their in-depth and detailed investigations. However, there is no systematic visual analysis of the gut-liver axis.

Bibliometrics is a literature analysis method that analyzes the output and status of publications in a particular research field from a quantitative and qualitative perspective [11]. This approach is considered an advanced method for understanding the developmental stages in various emerging disciplines [12]. Such literature visualization networks can potentially summarize and analyze the development process and the knowledge structure in the dimensions of time and space [13]. In this study, the knowledge maps of the gut-liver axis were generated using different bibliometric software to comprehensively demonstrate the collaboration network among representative countries and institutions, as well as to provide a convenient and flexible method to identify and track emerging trends.

2. Methods

2.1. Data source and search strategy

Literature data were collected from the Science Citation Index (SCI) of the Web of Science core database. Web of Science covered over 12000 high-quality scientific journals worldwide and had a relatively reliable database, making it the most suitable database for bibliometric analysis [14,15]. The search strategy used was as follows: [TS = ("gut liver axis" OR "gut-liver axis")] AND [Language = (English)] AND [document type = ("article" OR "review")]. The retrieval time was limited from January 1, 1998 to December 31, 2022. The following exclusion criteria were used to screen the obtained literature: articles not officially published, publications of meeting summary and meeting minutes, early online publications, repeated articles unrelated to the topic, book chapters, and incomplete articles. The dataset retrieved from the Web of Science was downloaded, set as plain and tab-delimited text format, and subsequently exported as the "Full Record and Cited References". Two researchers (YW and TZ) independently extracted relevant

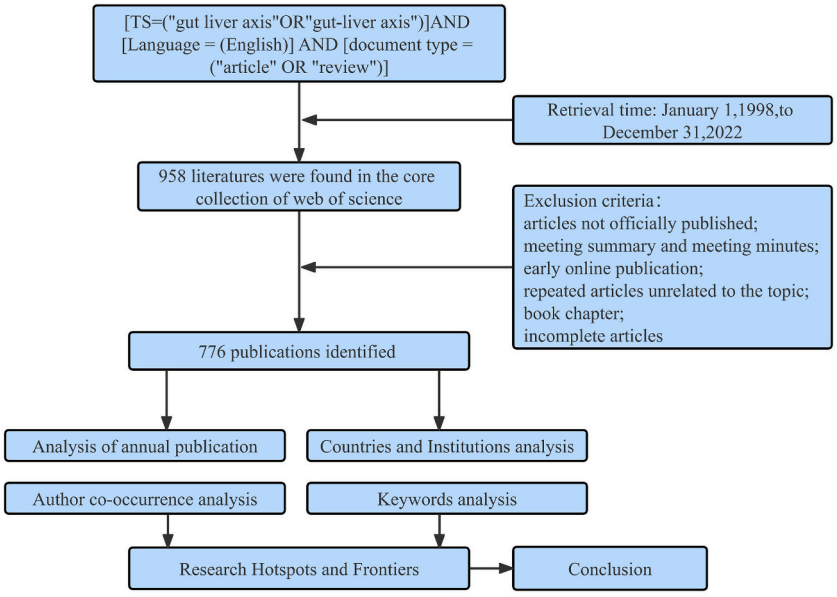


Fig. 1. Strategy for data search and analysis.

records from screened articles and saved them as plain text files on Jan 15, 2023, including titles, keywords, authors, institutions, journals, publication dates, countries/regions, citations, etc. Finally, 776 publications were identified. Fig. 1 shows the steps involved in the screening and data analysis process.

2.2. Data analysis

CiteSpace is a visualization software developed by Professor Chaomei Che that runs using the Java language environment and focuses on finding key and turning points in emerging disciplines [16]. This visualization software is widely popular for visualizing the knowledge structure, distribution, and evolution of a given domain [17,18]. In our research, CiteSpace was mainly used to analyze countries, institutions, co-cited journals, and keywords. In the co-occurrence network produced by CiteSpace, node size represents the frequency of occurrence, while the line density between the nodes denotes the proximity of cooperation.

VOSviewer [19] is another bibliometric software developed by Professor Nees Jan van Eck and Professor Ludo Waltman of Leiden University in the Netherlands. This software tool has text-mining capabilities and can extract key elements from many scientific publications for constructing and visualizing literature. In our study, we employed VOSviewer to evaluate the author collaboration relationship. The node size and color indicate the number and classification of these items, respectively, whereas the line thickness reflects the degree of cooperation between the authors.

Additionally, Scimago Graphica, a bibliometric mapping software [20], was applied to assess the national cooperative relationships. Microsoft Office Excel 2019 was used for the quantitative analysis of the publications.

3. Results

3.1. Number and category of publications

The number of annual publications and citations represents the development trend and potential of a field to a certain extent, including the level of attention paid to it by researchers. From the outset of the research concept of the gut-liver axis, 776 articles over the past 25 years met the retrieval requirements of our study. Fig. 2A intuitively displays the number of publications published and the number of citations in each year using histograms and line charts. The graphical data clearly show that the number of publications on the gut-liver axis has increased significantly in the past 3 years (2020–2022), while the number of citations has also increased significantly after 2018, reaching 6373 citations in 2022. The discussion and research on the gut-liver axis have therefore rapidly

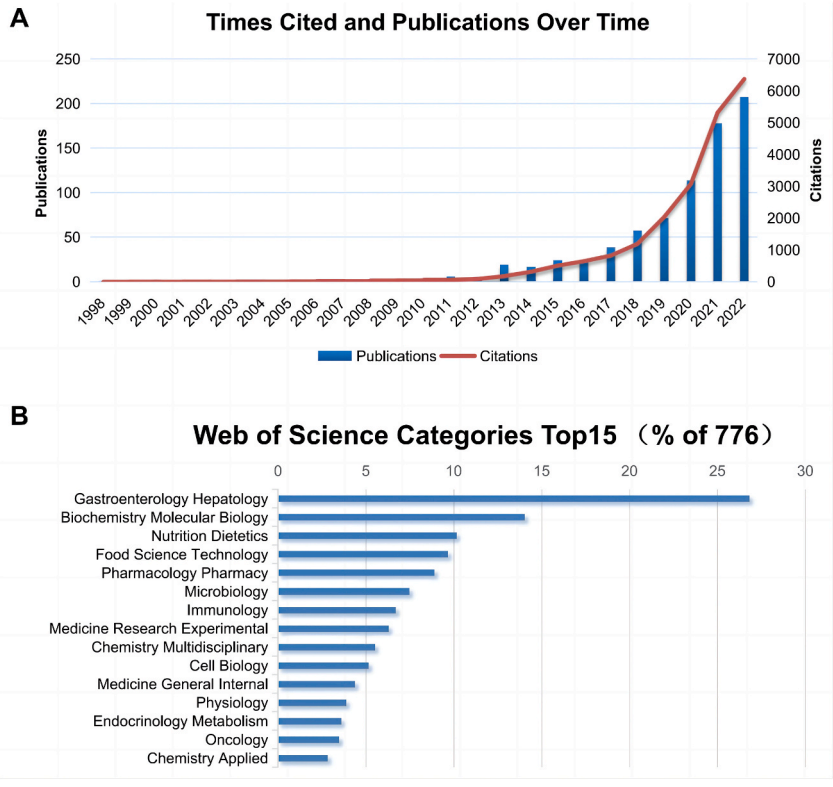


Fig. 2. Number of publications and categories. (A) Number of times cited and publications over time. (B) The top 15 categories according to the Web of Science classification results (% of the total 776 articles).

developed in the last 5 years. Thus, the gut-liver axis has become a relatively cutting-edge and hot topic.

According to the classification results of the Web of Science (Fig. 2B) for the 776 articles related to the gut-liver axis, the diseases and scope of research were mainly focused on topics including gastroenterology, hepatology, biochemistry, molecular biology, nutrition dietetics, food science and technology, pharmacology, and microbiology. Among them, gastroenterology and hepatology were the hot topics, accounting for 26.80% of the articles.

3.2. Visual analysis of gut-liver axis research in countries and institutions

To evaluate the development level of the gut-liver axis field in different countries and institutions and to identify the degree of their potential cooperative relationships, we changed the node type in CiteSpace to "country" and constructed co-occurrence networks for countries and institutions researching the gut-liver axis. Furthermore, we used Scimago Graphica to present the countries and their cooperative relationships in the form of maps. Fig. 3A and C shows the interaction network of the countries studying the gut-liver axis. The national network generated by CiteSpace comprised 54 nodes and 157 links and had a density of 0.1097, indicating that many countries were involved in exploring the gut-liver axis and maintaining close international cooperation. In this network, the top five prominent nodes were the United States, China, Italy, Germany, and Spain, demonstrating that these nations were at a world-leading level in the field of the gut-liver axis, with relatively obvious (centrality >0.10) cooperative relationships among them. Although the United States did not have the highest number of published articles, it had the highest centrality score of 0.45. This could be because the United States began researching the concept of the gut-liver axis 2 years after its inception in 1998, thereby maintaining a high level of centrality. However, China initiated its research in this field as late as 2009. However, it had the highest number of publications (267 articles, 34.4%) and the second-highest centrality. Thus, China's contribution to the study of the gut-liver axis is noteworthy

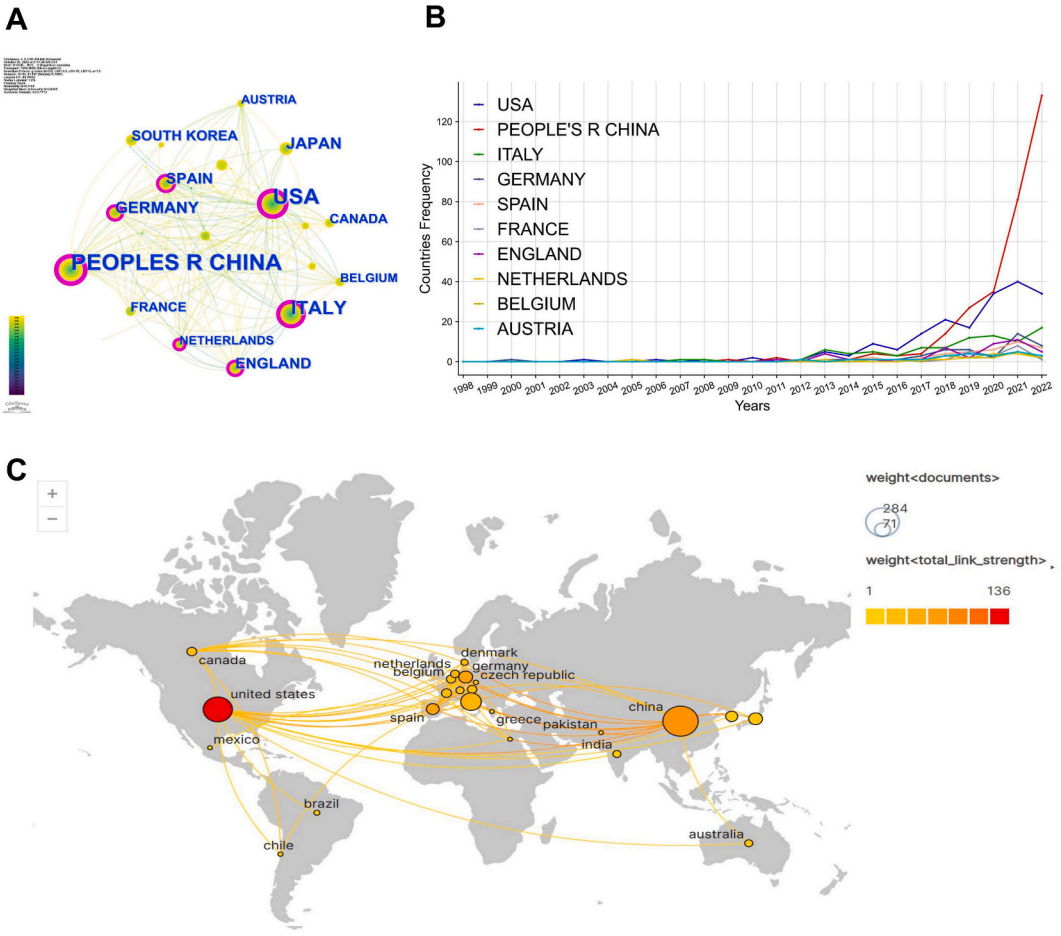


Fig. 3. Visual analysis of gut-liver axis research according to countries. (A) The collaboration network of the major countries studying the gut-liver axis. The size of the nodes in the graph represents the number of publications in the respective country, while the different colors of the inner circle and the connection line represent the different years. Nodes with purple rings indicate centrality greater than 0.1. (B) The number and growth trend of annual publications in the top 10 countries. (C) A world map showing the number of publications and the strength of the collaborations among the countries. The size of the nodes in the graph denotes the number of publications in the respective country, whereas the yellow to red colors reflect the link strength. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(Fig. 3B–Table 1).

Our analysis showed that some countries were relatively early in paying attention to and implementing research on the gut-liver axis. After several years of development, these countries have established several active academic groups. Next, we changed the node type in CiteSpace to "institution" and created a co-occurrence network of global institutions (Fig. 4A). The network consisted of 323 nodes and 349 links with a density of 0.0067, revealing that many institutions were conducting research on the gut-liver axis. Among these institutions, the University of California San Diego in the United States contributed the most articles and had a high centrality score. Fig. 4B intuitively displays top 20 institutions with strong cooperative relationships. We can see that the cooperation between the University of California San Diego and VA San Diego Healthcare System is strong. In contrast, other institutions had relatively few research publications and weak cooperation in the field of the gut-liver axis (Fig. 4B–Table 2).

3.3. Analysis of principal investigators and co-cited journals

We analyzed the main investigators studying the gut-liver axis using the author co-occurrence density diagram. We can see that the density of authors is scattered and relatively independent of each other, indicating a weak cooperative relationship (Fig. 5A, Table 3). Suk, Ki Tae and Schnabl, Bernd were tied for the first rank in most publications, with 13 articles each, whereas the number of articles published by the remaining authors was quite similar (Fig. 5B–Table 3).

The dual-map overlay of journals (Fig. 6) shows the position of the studies related to the gut-liver axis with respect to the major disciplines. Each point on the map represents a journal. The left side of the map presents the citing map, the right depicts the cited map, and the curve represents the citation line. The dual-map overlay of journals completely displays the context of the citation. Fig. 6 shows that publications in the MOLECULAR, BIOLOGY, and IMMUNOLOGY fields are mainly influenced by publications in the MOLECULAR, BIOLOGY, and GENETICS ($z = 4.45$, $f = 9148$) fields and HEALTH, NURSING, and MEDICINE ($z = 1.71$, $f = 3932$) fields (orange trajectory). Furthermore, articles published in the MEDICINE, MEDICAL, and CLINICAL fields are mainly influenced by publications in the fields of MOLECULAR, BIOLOGY, and GENETICS ($z = 4.44$, $f = 9126$) and HEALTH, NURSING, and MEDICINE ($z = 1.28$, $f = 5034$) (green trajectory). The dual-map overlay suggests that current research on the gut-liver axis is mainly focused on the molecular, biology, and genetics fields.

3.4. Keywords

CiteSpace is used to analyze the co-occurrence, clustering, and occurrence time of keywords, which helps understand the research hotspot, frontier, and trend in a field. Using the co-occurrence of the keywords and cluster analysis of the gut-liver axis research (Fig. 7A), we found 507 nodes and 1213 links, with a Q value of 0.7558 ($Q > 0.3$) and an S value of 0.8868 ($S > 0.5$). These results indicated that the clustering model was significant and could be used for analysis [21]. From Fig. 7A and Table 4, we identified "gut microbiota," "inflammation," "bile acid," "insulin resistance," "non-alcoholic steatohepatitis," "oxidative stress," "hepatic steatosis," "bacterial translocation," "obesity," and "hepatocellular carcinoma," as well as other popular keywords in the studies on the gut-liver axis. Additionally, the clustering of these keywords and the selection of the top six clusters were performed for a more appropriate analysis based on the overlapping area of the clustering options. The top six clusters obtained were as follows: #0 liver dysfunction, #1 cystic fibrosis, #2 hepatic drug metabolism, #3 or steatohepatitis, #4 sensing microbe, and #5 liver diseases.

Due to the continuous development in a research field, the research hotspots will inevitably change over time. Consequently, simply relying on the frequency of keyword occurrences entails considerable limitations. Keyword clustering analysis should be combined with time scales to more accurately distinguish the cutting-edge fields in a domain [21]. Therefore, we plotted the timeline and keywords with bursts using CiteSpace (Fig. 7B and C). From 1998 to 2010, research on the gut-liver axis was mainly focused on liver disease mechanism, Kupffer cell, immune response, hepatic steatosis, insulin resistance, intrinsic permanence, primary sclerosing cholangitis, and bile acid. From 2010 to 2020, gut-liver axis research was concentrated on gut microbiota, increased intestinal permeability, hepatocellular carcinoma, inflammation, obesity, fatty liver, diet, farnesoid X receptor, and toll-like receptor. Finally, the keywords used from 2020 to 2022 were crucial and reasonably reflected research trends. Apart from gut microbiota remaining a hot topic, research on the gut-liver axis tended to be mostly focused on liver cirrhosis, induced obesity, alcohol-associated liver disease,

Table 1
Top 10 countries with the most publications in "gut-liver axis" research.

Rank	Country	Frequency	Centrality	Starting year
1	USA	190	0.45	2000
2	PEOPLE'S R CHINA	267	0.44	2009
3	ITALY	96	0.28	2005
4	GERMANY	43	0.13	2000
5	SPAIN	37	0.11	2014
6	FRANCE	23	0.07	2013
7	ENGLAND	33	0.17	2011
8	NETHERLANDS	17	0.11	2005
9	BELGIUM	20	0.04	2015
10	AUSTRIA	19	0.02	2012

USA, United States of America, PEOPLE'S R CHINA, People's Republic of China.

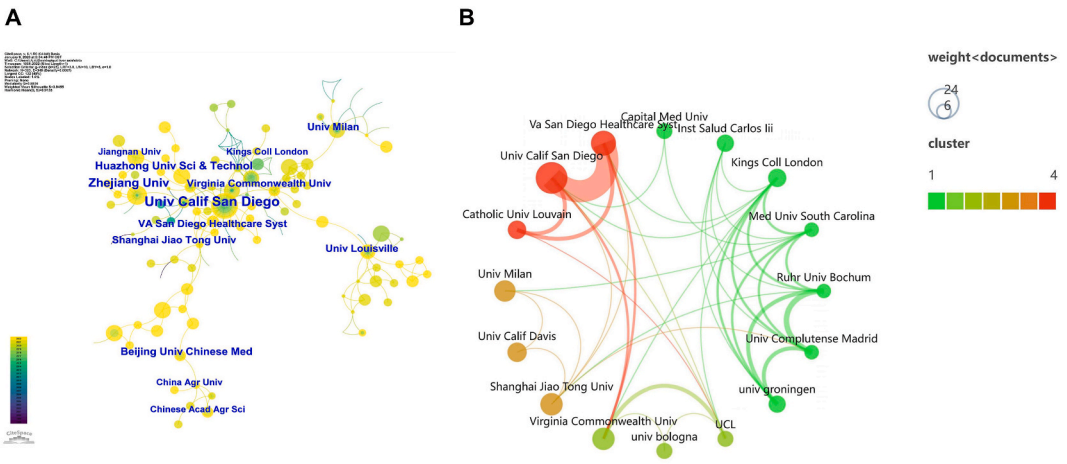


Fig. 4. The co-occurrence of institutions. (A) A collaboration network of the major institutions studying the gut-liver axis. The size of the nodes in the graph represents the number of publications in the respective institution, while the different colors of the inner circle and the connection line denote the different years. (B) Top 20 institutions with strong cooperative relationships. The size of the circle represents the number of papers publications by different institutions; The thickness of the connections between different institutions represents the strength of their cooperation; Institutions with the same color may have strong partnerships. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Top 10 institutions with the most publications in the field of the "gut-liver axis."

Rank	Institutions	Publications	Centrality
1	Univ Calif San Diego	23	0.19
2	Zhejiang Univ	16	0.03
3	Hallym Univ	15	0
4	Huazhong Univ Sci & Technol	12	0.02
5	Beijing Univ Chinese Med	10	0.04
6	Virginia Commonwealth Univ	9	0.02
7	VA San Diego Healthcare Syst	9	0.02
8	Univ Milan	9	0.06
9	Univ Louisville	9	0.11
10	Shanghai Jiao Tong Univ	9	0.06

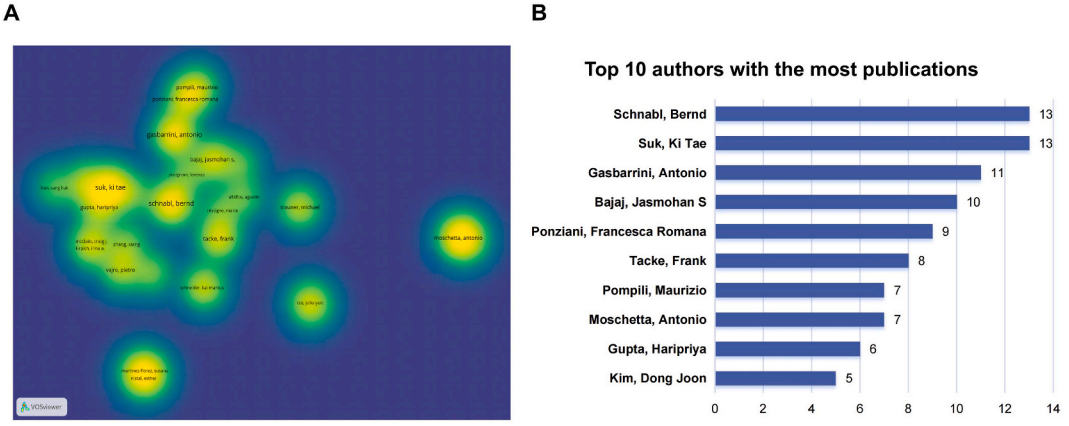


Fig. 5. The co-occurrence of authors. (A) A VOSViewer-generated density map of authors involved in "gut-liver axis" research. The larger the number of publications in the neighborhood of a point and the higher the weights of the neighboring publications, the closer the color of the point is to yellow. (B) Top 10 authors with the most publications. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Top 10 most productive authors with the most publications in the "gut-liver axis" field.

Rank	Author	Frequency	Centrality
1	Suk, Ki Tae	13	0
2	Schnabl, Bernd	13	0
3	Gasbarrini, Antonio	11	0
4	Bajaj, Jasmohan S	10	0
5	Ponziani, Francesca Romana	9	0
6	Tacke, Frank	8	0
7	Moschetta, Antonio	7	0
8	Pompili, Maurizio	7	0
9	Gupta, Haripriya	6	0
10	Kim, Dong Joon	5	0

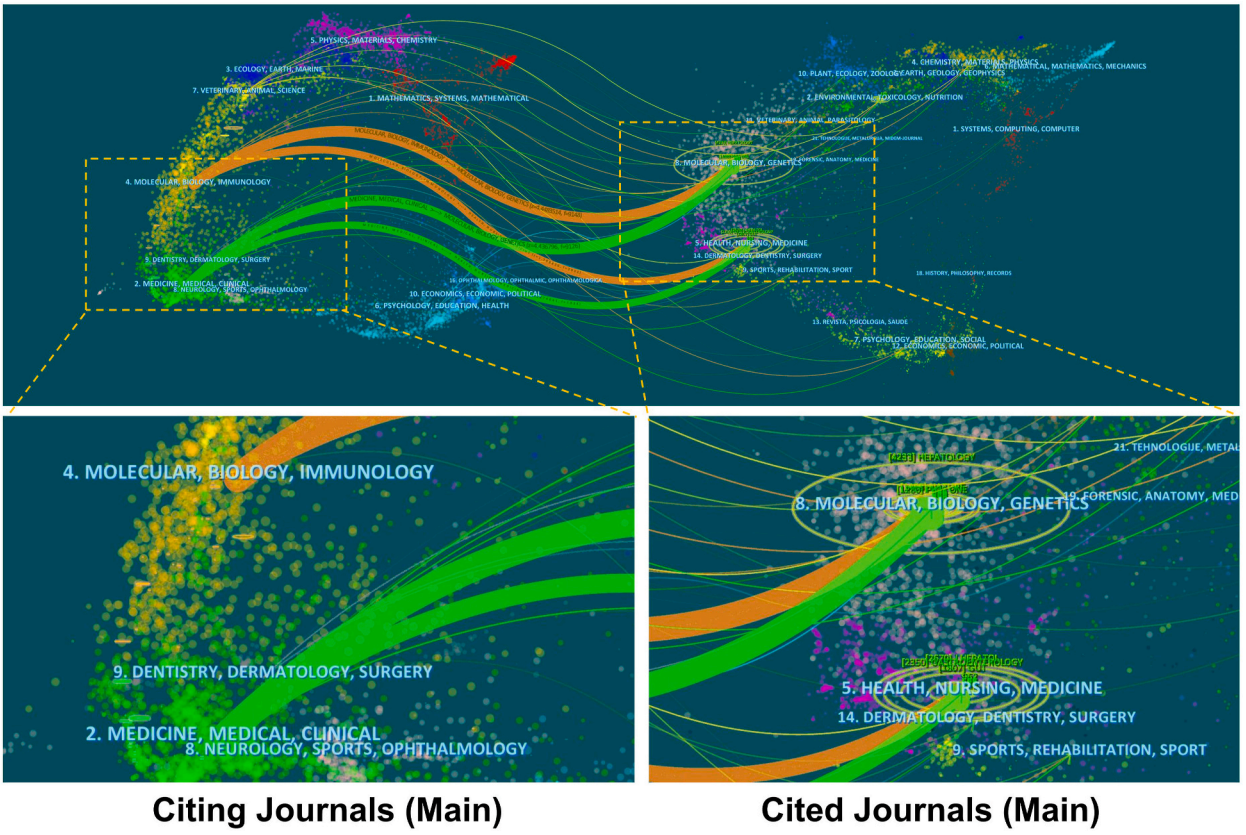


Fig. 6. Dual-map overlay of the journals on gut-live axis research (1998–2022). Each point on the map represents a journal. The left side of the map shows the citing journals, and the right part presents the cited journals. Colored paths represent reference relationships, with thicker lines represent the main paths.

metabolic disease, host metabolism, and drug metabolism (Fig. 7C).

Keywords with bursts can better reflect the changes in some important keywords over time to determine research trends (Fig. 7B). From the list of keywords with bursts, bacterial translation and tumor necrosis factor (including tumor necrosis factor alpha) were observed to be research hotspots from when the concept of the gut-liver axis was proposed up to 2018, while gut microbiota continued to be a hot topic. From 2011 to 2020, the research hotspots were non-alcoholic steatohepatitis (including non-alcoholic fatty liver disease), insulin resistance, metabolic syndrome, portal hypertension, primary sclerosing cholangitis, and primary biliary cirrhosis. In terms of the mechanisms, the research hotspots included increased intestinal permeability, bile acid receptor, and toll-like receptor. From 2018 to 2022, gut microbiota and fecal metabolites remained hot research topics. Furthermore, clinical trials and double-blind studies have been involved in the research on non-alcoholic steatohepatitis, reflecting a transition from basic concepts to clinical practice.

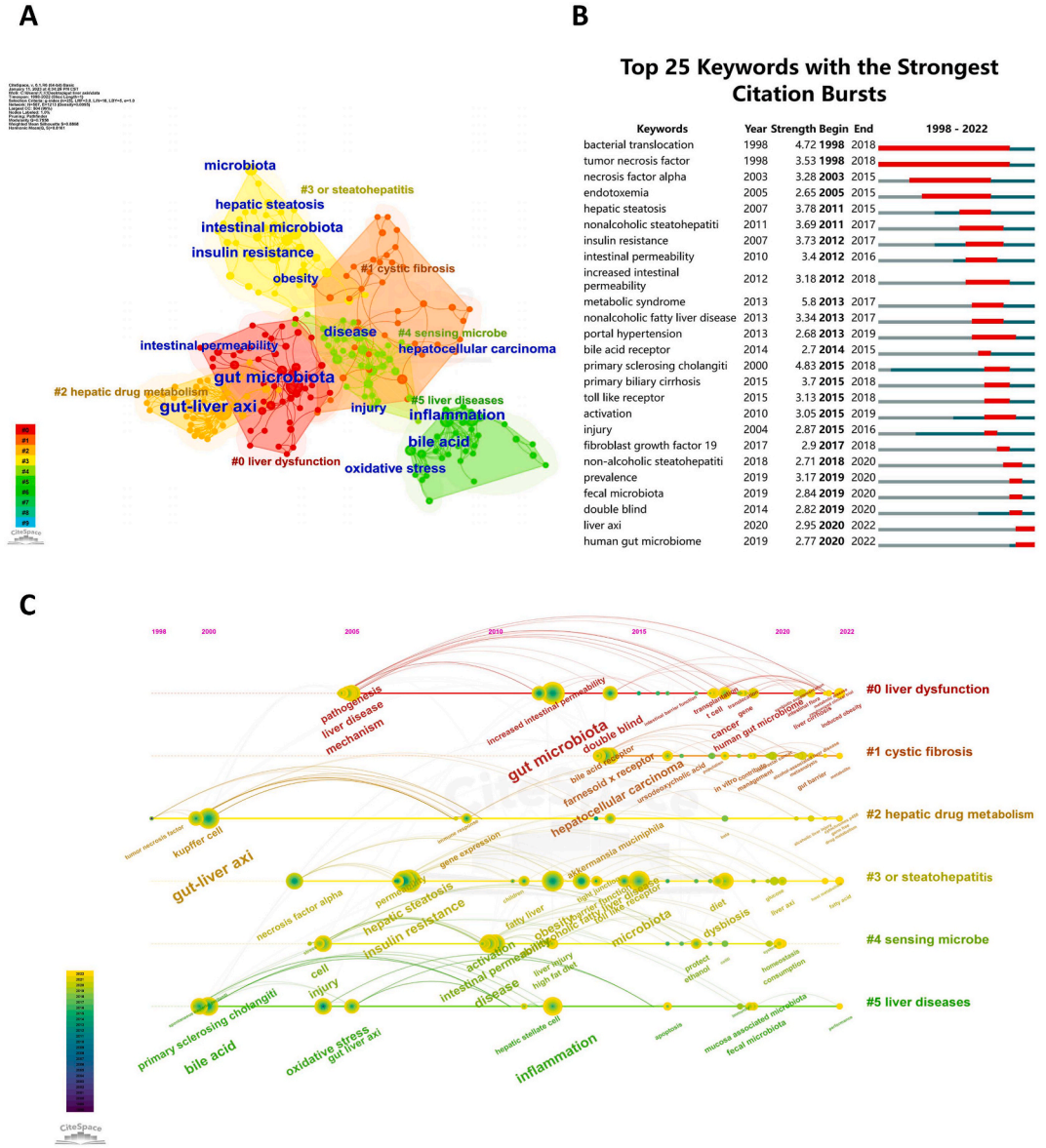


Fig. 7. Keyword co-occurrence analysis. (A) The top 5 clusters of keywords. Each color region represents a cluster, and each node denotes a keyword. Areas with the same color represent a cluster with the same topic. Silhouette S = 0.8868. Modularity Q = 0.7558. (B) Top 25 keywords with the strongest citation bursts from 1998 to 2022. The "Strength" represents the strength of citation bursts. The red segment represents the begin and end year of the burst duration. (C) Timeline view of the keywords in gut-liver axis research. Each circle represents a keyword, and circles on the same line represent a cluster with the same topic. The position of each circle represents the time it first appeared. The size of the circle is proportional to the frequency of keyword occurrences. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.5. Analysis of co-cited references

Reference co-citation analysis was another way to analyze the knowledge base and trace developmental process in a certain research field [22,23]. We changed the node type in CiteSpace to "reference" and created a co-occurrence network (Fig. 8A), which consisted of 917 nodes and 2409 links with a density of 0.0057. Among these references, the top two were cited more than 100 times, and were important references to guide gut-liver axis research (Supplementary Table 1). In addition, we constructed the network map of co-cited references including 917 references to visualize the key 16 clusters of co-cited references (Fig. 8B). The modularity Q score of the clustering map was 0.8119, indicating the network structure of the map was good. Moreover, the weighted S value was 0.8841, indicating it had consistent clustering effectiveness and reliable quality. Cluster #0, "microbial metabolite," was the largest cluster in the visualization center, followed by "alcohol-related liver disease" (cluster #1), "nonalcoholic steatohepatitis" (cluster #2) and

Table 4
Top 15 keywords in the publications on the "gut-liver axis" according to frequency.

Rank	Keywords	Frequency	Centrality
1	gut-liver axis	271	0.16
2	gut microbiota	246	0.01
3	inflammation	140	0
4	bile acid	130	0.28
5	insulin resistance	105	0.03
6	intestinal microbiota	91	0.01
7	microbiota	88	0
8	non-alcoholic steatohepatitis	82	0.02
9	oxidative stress	67	0.03
10	hepatic steatosis	65	0.11
11	bacterial translocation	64	0.36
12	obesity	63	0.03
13	hepatocellular carcinoma	62	0.02
14	intestinal permeability	59	0.06
15	activation	56	0.02

"bacterial translocation" (cluster #3). There were four main types of topics in the study of the gut-liver axis, which were more specific than the results of keyword analysis.

To better understand the developmental process of gut-liver axis research over the past 25 years, references with strong citation bursts were identified by CiteSpace. Fig. 8C presented the top 25 references with the strongest citation bursts from 1998 to 2022. Among them, references with citation bursts first appeared in 2011, stemming from a study published in 2009. "Henao-Mejia J, 2012, NATURE, V482, P179″, "Schnabl B, 2014, GASTROENTEROLOGY. V146, P1513″ and "Qin N,2014, NATURE, V513, P59″ were among the top three references, all of which were review articles on gut microbiota and liver disease published in prestigious journals [24–26], with the strongest burst strength (15.51, 14.46, and 13.42, respectively). Of note, there was one recent reference with citation bursts beginning from 2018, and the bursts are still ongoing. It was an article about intellectual crosstalk between bill acids and microbiota [27], indicating that the crosstalk between bile acids metabolism and gut microbiota was currently a hot research topic.

4. Discussion

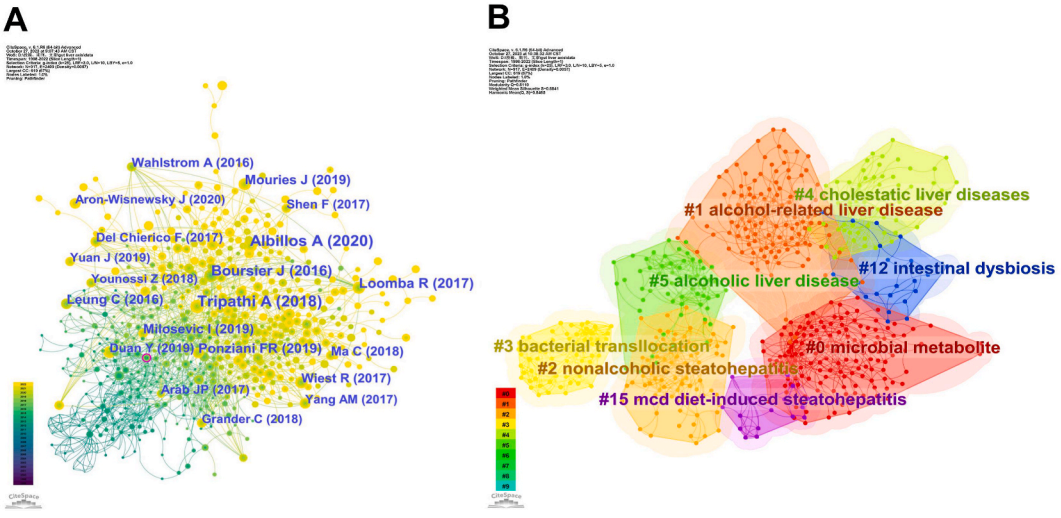
4.1. The global research dynamics in the field of gut-liver axis

The number of publications in a certain field can reflect the productivity and development of the topic over the years. The concept of gut-liver axis has become a hot topic in the field of digestive research since it was proposed by Marshall in 1998. However, according to the results of this bibliometric analysis, both the number of articles published and the frequency of citations have shown a clear trend of gradual increase in recent years, as the key role of gut-liver axis disorders in the pathogenesis of many liver diseases has only recently been accepted and become a hot topic in academic research.

At the national level, some countries started gut-liver axis research earlier and had a dominant position in terms of the number of published articles, which may be influenced by regional and temporal differences in the incidence of liver diseases. For example, an epidemiological survey in the United States in 2004 showed that one in three American adults had liver steatosis [29]. A systematic review in 2019 showed that the regions with the highest prevalence of NAFLD were South America and North America (35.7% and 35.3%, respectively) [30]. These results may directly lead to increased attention on the gut-liver axis in the United States. NAFLD had previously been considered uncommon in the Asia-Pacific region because it was thought to be a disorder of affluence, where the burden of viral hepatitis was heavy [31]. Until recently, the major risk factors of NAFLD, such as type 2 diabetes, obesity, dyslipidemia and metabolic syndrome, were widely prevalent in the Asia–Pacific region and were increasing in geometric proportion [32,33]. These factors may have led China to start paying attention to gut-liver axis research from 2019 and become the country with the highest number of published articles. However, it should be emphasized that there was not much cooperation between various institutions and authors in global research on the gut-liver axis, and further cooperation and communication were needed to promote in-depth research on the gut-liver axis.

4.2. Intestinal permeability and bacterial translocation remains a hot topic in gut-liver axis studies

Keywords reflect the core theme and main content of the article, enabling them to provide a reasonable notion of research hotspots [34]. Gut microbiota is one of the current research hotspots, and the role of gut microbiota in maintaining host health has attracted considerable attention for a long time [35]. Scientific research has revealed a connection between microbial imbalance or disorder and diseases that affect not only the intestines but also organs such as the brain, liver, lungs, and kidneys [36]. In terms of the gut microbiota and liver, the close interaction between the portal vein system and intestinal lymphatic tissue and the liver has led to the involvement of gut microbiota in the occurrence and development of metabolism- and immune-related liver diseases. Under conditions such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), liver fibrosis, liver cancer, and other similar diseases, this huge "intestinal bacterial organ" affects the integrity and immune activation level of local intestinal mucosa via the mechanisms of



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Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1998 - 2022
Miele L, 2009, HEPATOLOGY, V49, P1877, DOI 10.1002/hep.22848, DOI	2009	10.06	2011	2014	
Velayudham A, 2009, HEPATOLOGY, V49, P989, DOI 10.1002/hep.22711, DOI	2009	7.54	2011	2014	
Aller R, 2011, EUR REV MED PHARMACO, V15, P1090	2011	5.49	2012	2015	
Henao-Mejia J, 2012, NATURE, V482, P179, DOI 10.1038/nature10809, DOI	2012	15.51	2013	2017	
Zhu LX, 2013, HEPATOLOGY, V57, P601, DOI 10.1002/hep.26093, DOI	2013	12.31	2013	2018	
Compare D, 2012, NUTR METAB CARDIOVAS, V22, P471, DOI 10.1016/j.numecd.2012.02.007, DOI	2012	7.73	2013	2017	
DeMinicis S, 2014, HEPATOLOGY, V59, P1738, DOI 10.1002/hep.26695, DOI	2014	6.35	2014	2019	
Bull-Otterson L, 2013, PLOS ONE, V8, P0, DOI 10.1371/journal.pone.0053028, DOI	2013	6.35	2014	2017	
Alisi A, 2014, ALIMENT PHARM THER, V39, P1276, DOI 10.1111/apt.12758, DOI	2014	5.93	2014	2019	
Mouzaki M, 2013, HEPATOLOGY, V58, P120, DOI 10.1002/hep.26319, DOI	2013	5.68	2014	2018	
Yoshimoto S, 2013, NATURE, V499, P97, DOI 10.1038/nature12347, DOI	2013	5.68	2014	2018	
Schnabl B, 2014, GASTROENTEROLOGY, V146, P1513, DOI 10.1053/j.gastro.2014.01.020, DOI	2014	14.46	2015	2019	
Balmer ML, 2014, SCI TRANSL MED, V6, P0, DOI 10.1126/scitranslmed.3008618, DOI	2014	6.75	2015	2019	
Everard A, 2013, P NATL ACAD SCI USA, V110, P9066, DOI 10.1073/pnas.1219451110, DOI	2013	6.51	2015	2018	
Sayin SI, 2013, CELL METAB, V17, P225, DOI 10.1016/j.cmet.2013.01.003, DOI	2013	5.97	2015	2018	
Neuschwander-Tetri BA, 2015, LANCET, V385, P956, DOI 10.1016/S0140-6736(14)61933-4, DOI	2015	10.98	2016	2020	
Szabo G, 2015, GASTROENTEROLOGY, V148, P30, DOI 10.1053/j.gastro.2014.10.042, DOI	2015	9.31	2016	2020	
Spadoni I, 2015, SCIENCE, V350, P830, DOI 10.1126/science.aad0135, DOI	2015	6.64	2016	2020	
Jiang CT, 2015, J CLIN INVEST, V125, P386, DOI 10.1172/JCI76738, DOI	2015	6.3	2016	2020	
Qin N, 2014, NATURE, V513, P59, DOI 10.1038/nature13568, DOI	2014	13.42	2017	2019	
Bajaj JS, 2014, J HEPATOL, V60, P940, DOI 10.1016/j.jhep.2013.12.019, DOI	2014	8.93	2017	2019	
Boursier J, 2016, HEPATOLOGY, V63, P764, DOI 10.1002/hep.28356, DOI	2016	7.51	2017	2020	
Leclercq S, 2014, P NATL ACAD SCI USA, V111, PE4485, DOI 10.1073/pnas.1415174111, DOI	2014	5.45	2017	2019	
Chassaing B, 2014, HEPATOLOGY, V59, P328, DOI 10.1002/hep.26494, DOI	2014	7.28	2018	2019	
Wahlstrom A, 2016, CELL METAB, V24, P41, DOI 10.1016/j.cmet.2016.05.005, DOI	2016	6.1	2018	2022	

Fig. 8. Co-cited references and burst references. (A) The network map of co-cited references. Nodes in the visualized network represent co-cited references. Lines between nodes represent co-cited links. (B) The network map of co-cited clusters. 16 clusters with diversified research themes were formed and illustrated in different colors. Areas with the same color represent a cluster with the same topic. Silhouette S = 0.8841. Modularity Q = 0.8119. (C) Top 25 references with the strongest citation burst in the gut-liver axis field from 1998-2022. The "Strength" represents the strength of citation bursts. The red segment represents the begin and end year of the burst duration. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

nutrient absorption and material metabolism as well as the self-secretion of numerous inorganic compounds (such as butyric acid and ethanol) and organic substances (e.g., multiple bacteria-derived peptide products), thereby facilitating the occurrence of diseases [37,38].

Based on the keywords with bursts and citation analysis, bacterial translocation and intestinal permeability were demonstrated to be continuously trending keywords. Bacterial translocation can be attributed to intestinal mucosal barrier damage, a prerequisite for alterations in the gut-liver axis [39]. Consequently, intestinal mucosal barrier damage and increased intestinal permeability were hot research topics in the disruption mechanism of the gut-liver axis, covering the entire history of gut-liver axis research. The intestinal mucosal barrier is a large, precise three-dimensional defense system comprising mechanical, chemical, immunological, and microbiological barriers. This intestinal barrier can prevent various bacteria, endotoxins, and harmful metabolites in the intestine from migrating outside the intestinal cavity and is our first line of defense against exogenous substances. Intestinal mucosal barrier damage can be caused by factors such as diet [40,41], gut microbiota [42], and immune mediators [43,44]. Damage to the integrity of the intestinal mucosal barrier via atrophy, injury, and/or imbalance of gut microbiota can lead to the translocation of bacteria and

endotoxins into the bloodstream, thereby damaging the liver and exacerbating the conditions of systemic inflammatory reaction and multiple organ dysfunction [37]. Endotoxins are pathogen-associated molecular patterns (PAMPs) derived from Gram-negative bacterial walls. Endotoxins and toll-like receptor 4 (TLR4) can induce macrophages to release pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-1 β [45,46]. Furthermore, endotoxemia has been reported to be a contributing factor to systemic low-grade inflammation in metabolic diseases, such as type 2 diabetes, obesity, and NAFLD. In addition to endotoxins, PAMPs, including lipoglycans, peptidoglycans, lipopeptides, or DNA from viruses and bacteria, may reach the liver via the portal vein [47].

Moreover, mucosal barrier damage allows bacterial metabolites to easily enter the host and exert their effects through the intestine-liver axis. In patients with type 2 diabetes, the concentration of imidazole propionate, a bacterial metabolite, increases in the portal venous blood, which impairs the insulin signal transduction by activating P38 MAPK and P62 phosphorylation, leading to increased mTOR activity [48]. In experimental NAFLD mice, phenylacetate, an intestinal symbiotic metabolite, was shown to cause liver steatosis, while fecal transplantation from patients with obesity to mice was revealed to aggravate liver steatosis [49]. Additionally, the gut microbiome has been reported to control the transcription profile of the liver endothelium through undefined metabolites [50].

4.3. Disruption of the gut-liver axis by metabolic disorders of the gut microbiota and host may be a future research trend

The keywords timeline shows that "metabolism" had the highest frequency in 2022 among all other keywords, indicating that "metabolism" will play a key role in future research on the gut-liver axis. The liver is an important human metabolic organ, and as shown in Fig. 9, many liver diseases are associated with metabolism. NAFLD prevalence is rising globally, partly due to the prevalence of metabolic diseases, such as insulin resistance, type 2 diabetes, and overweight or obesity [51]. Furthermore, alcohol and high-fat and high-fructose diets can promote intestinal permeability, allowing microorganisms to migrate from the intestine to the liver [52–55]. In addition, the host's metabolism status, including drug and dietary metabolism, can affect the gut microbiota. The gut microbiota antigens and disordered metabolites can exacerbate liver inflammation and fibrosis, causing circulatory effects [56].

Bile acid metabolism played an important role in gut-liver axis studies. Both keyword analysis and citation analysis suggest that bile acid (BA) metabolism is currently a hot topic in gut-liver axis studies. BA is synthesized by cholesterol in liver cells, which is further combined with taurine or glycine, excreted into bile, and metabolized into secondary BA by gut microbiota. The primary and secondary BAs are reabsorbed in the small and large intestines and then return to the liver through the portal venous blood. This

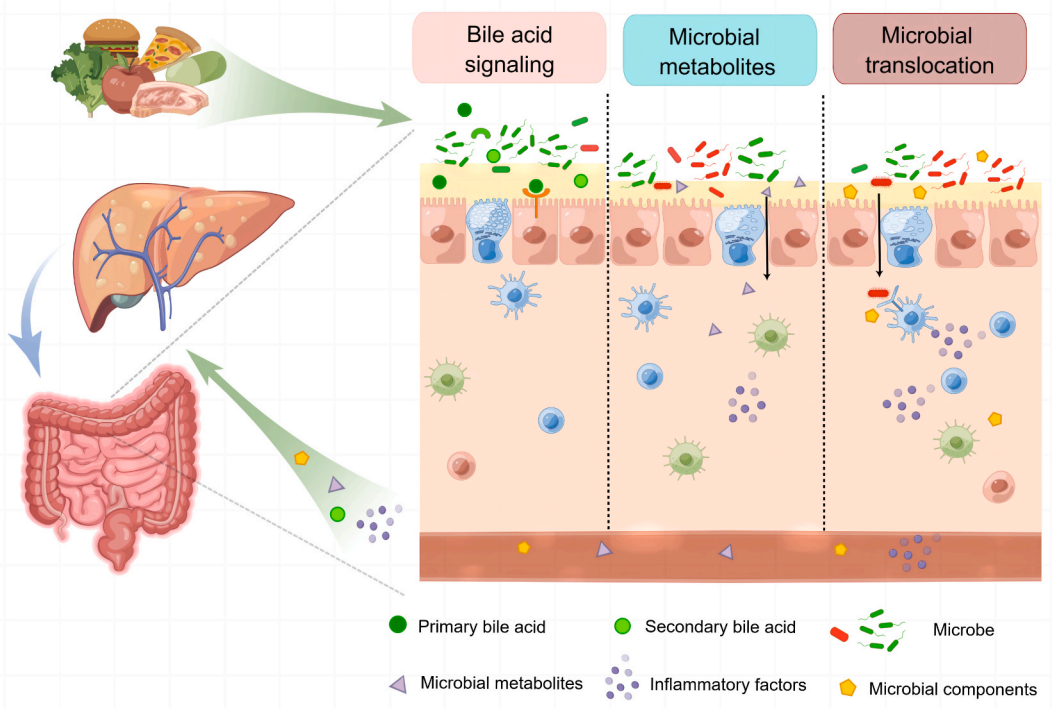

Fig. 9. Disruption of the "gut liver axis" by metabolic disorders. Patients with liver diseases such as NAFLD often exhibit altered bile acid profiles and intestinal barrier function. Primary bile acids are synthesized in the liver and secreted into the gut, where microbes transform primary bile acids into secondary bile acids. Most of the bile acids are reabsorbed in the small intestine and transported to the liver via the hepatic portal vein, a process known as enterohepatic circulation. Secondary bile acids can bind to receptors such as FXR in the intestine and liver, shaping epithelial barrier function and liver metabolism. Barrier damage promotes abnormal escape of gut microbes, or microbial components, a process known as bacterial translocation. LPS is a bacterial endotoxin that can trigger an inflammatory response [28].

enterohepatic circulation is completed several times (4–12 times) a day [57,58]. BA plays a crucial role in the emulsification and absorption of dietary fats, cholesterol, and fat-soluble vitamins and has been identified as an important signal molecule in the metabolism of lipids, glucose, and energy [59,60]. Following the discovery of the first BA farnesoid X receptor (FXR) in 1999, BA has been widely studied for its role as a key signaling molecule and involvement in various physiological and pathological processes [61]. BA signals mediate the homeostasis of BA, lipids, and glucose through nuclear (hormone) receptors, such as FXR and GPCRs, and the control of innate/adaptive immunity. BA signals also perform the crucial functions of regulating liver metabolism, shaping gut microbiota, maintaining intestinal integrity, and preventing bacterial translocation [62–65]. Therefore, BA and its derivatives can be used as potential liver disease therapies. BA derivatives and signal mimics targeting FXR and downstream signaling pathways (e.g., fibroblast growth factor 15) have already been demonstrated as important strategies for treating cholestasis and metabolic liver diseases [66,67].

4.4. Exploring the pathogenesis and effective treatment methods of liver diseases is the main content of intestinal liver axis research

4.4.1. NAFLD

Based on the keyword timeline and keywords with bursts (Fig. 7B and C), NAFLD was the largest disease type in gut-liver axis research. This disease is a metabolic irritability-induced liver injury closely related to insulin resistance and genetic susceptibility [68]. The NAFLD spectrum covers simple hepatic steatosis, non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma. NAFLD is the main cause of liver diseases worldwide, affecting both adults and children, and will become the leading etiology of end-stage liver disease in the near future [68–70]. This liver disease has an extremely complex pathophysiology that involves many pathways, including insulin resistance, inflammation, lipotoxicity, increased de novo adipose formation, and oxidative stress [71]. In recent years, research on gut microbiota and gut-derived immune cells in NAFLD have provided strong evidence supporting the gut-liver axis theory [72]. In 2010, Tilg and Moschen proposed the "multiple hit theory," indicating that multiple factors simultaneously contribute to NAFLD occurrence, particularly the intestine- and adipose tissue-derived factors [73]. Furthermore, NAFLD occurrence was shown to cause an increase in intestinal mucosal permeability [74] and intestinal bacterial overgrowth [75]. Gut microbiota imbalance increases the influx of substances such as lipopolysaccharides and bacterial metabolites, which enter the liver through the portal vein, activate TLRs, and induce the release of inflammatory cytokines and chemokines [76–78]. The role of gut microbiota in NAFLD has also been demonstrated in mouse studies using fecal microbiota transplantation (FMT) or co-habitation experiments [79]. When the gut microbiota of mice fed on a high-fat diet were transplanted into sterile mice via FMT, the liver triglyceride content increased by three times and the expression of the liver lipogenesis genes significantly increased in the recipient mice [80,81]. Additionally, as previously mentioned, the mesenteric lymph node cells of NAFLD mice have been reported to migrate and aggregate in livers with adipose lesions, where these clustered immune cells are significantly activated and secrete pro-inflammatory cytokines, such as interferon [82,83]. All these results suggest that intestinal flora and immunological factors are involved in the development of NAFLD. A recent study has shown that high-density lipoprotein3 (HDL3), a form of HDL derived from the gut, passes through the portal vein in a complex with LPS-binding protein, preventing LPS from binding to liver macrophages and activating inflammation. Therefore, intra-intestinal HDL may be a suitable pharmacological target to protect the liver from gut-derived LPS leakage [84].

4.4.2. ALD

From the clustering analysis results of the citation, it can be seen that the occurrence of ALD was strengthened. During the pathogenesis of ALD, gut microbiota, changes in gut epithelial barrier, LPS/PAMPs, and changes in the gut-liver axis was important triggers. Multiple independent clinical studies suggested that excessive alcohol consumption can alter the gut microbiota, which was associated with mortality rates at 30 and 90 days in severe ALD [85]. Animal experiments have also shown that the increased intestinal mucosal barrier permeability, intestinal oxidative stress level and portal endotoxin level of mice after ethanol administration were related to the damage of the integrity of tight connections between intestinal epithelial cells by ethanol and its metabolites [86–88]. TLR4 gene knockout mice were also very susceptible to alcohol induced liver injury [89]. A recent study showed that the presence of cytolysin-positive *Enterococcus faecalis* in feces was associated with the severity of ALD, and targeting these bacteria with bacteriophages can improve its severity [90]. In addition, the abundance of *Akkermansia muciniphila* in ALD patients decreased, and supplementing this bacterium greatly improved ethanol-induced intestinal mucosal and liver damage in mice [91]. These studies provided new avenues for the treatment of ALD.

In addition to NAFLD and ALD being the focus of research, other liver diseases related to the gut-liver axis such as PSC, cirrhosis, and liver cancer were also reflected in the keywords analysis and citation clustering analysis. The common features of these studies were their focus on gut barrier damage, gut microbiota imbalance, and immune metabolic disorders.

Knowledge gained from studying the gut-liver axis in the past few years has raised the hope for treating previously untreatable liver diseases. Identifying the main damaged components in each chronic liver disease in the gut-liver axis provides possibilities for intervention. In addition to antibiotics, upcoming gut-centered therapies include new generations of probiotics, bacterial metabolites (postbiotics), fecal microbial transplantation, phages, and gut-restricted polymers or nanoparticles, providing new treatment options for these chronic liver diseases [39,92].

5. Limitations

Although our bibliometric analysis has provided a comprehensive perspective of the research field relevant to the gut-liver axis, it exists some limitations. First, the data was retrieved exclusively from the Web of Science database. Our retrieval strategy only included

some target objects related to the gut-liver axis, and excluded non-English articles that could lead to linguistic bias, all of which may have resulted in some publications being missed since no retrieval strategy is 100% accurate. Second, Although the literature screening was jointly completed by two researchers, biases caused by knowledge backgrounds, subjective judgments, and other reasons were unavoidable.

6. Conclusion

Our study is the first bibliometric analysis of literature using visualization software to present the current research status of the gut-liver axis over the past 25 years. The number of published papers has shown a significant upward trend, particularly in the past 3 years, indicating that the gut-liver axis has attracted a great interest from researchers around the world. Currently, hot topics of interest in the gut-liver axis research mainly focus on intestinal permeability, bacterial translocation, and bile acid metabolism, in order to explore the pathogenesis of chronic liver diseases and new treatment methods. Overall, this bibliometric analysis can provide valuable reference for researchers, as it can help them comprehensively understand the main contributors in the field of the gut-liver axis and discover ideas and inspiration for further research from hotspots and frontiers.

Ethics approval and consent to participate

This study did not require the approval of an ethics committee since we analyzed a secondary database.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Yongtian Wen: Writing – review & editing, Writing – original draft, Visualization, Software, Data curation. **Tai Zhang:** Writing – review & editing, Methodology, Data curation. **Beihua Zhang:** Writing – review & editing, Visualization, Project administration, Methodology. **Fengyun Wang:** Writing – review & editing, Project administration, Formal analysis. **Xiuxiu Wei:** Writing – review & editing, Visualization, Data curation. **Yuchen Wei:** Writing – review & editing, Visualization, Data curation. **Xiangxue Ma:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **Xudong Tang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27819.

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