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Research Article

A bibliometric analysis of lipid peroxidation in alcoholic liver disease from 2001 to 2024

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Abstract: Alcoholic liver disease (ALD) is the major liver disease burden among the world, and one of the most significant pathogenesis is lipid peroxidation (LPO), which has been shown to participate in a wide range of diseases. This study aimed to determine the status, research hotspots, and development trend of research on LPO in ALD. Based on the Web of Science Core Collection (WOSCC) and the China National Knowledge Infrastructure (CNKI) databases, the publication and quality of the article, cooperative network, citation, and keyword analysis were described by bibliometric analysis. The number of studies on LPO in ALD fluctuated over time. The largest number of articles was published in *Food and Chemical Toxicology*. China and USA were the two most published countries, with Zhi-Yun Chen (China) and Petersen DR (USA) being the most prolific researchers. Current research mainly includes the key products and pathway targets in diseases, as well as the exploration of drugs, including traditional chemical and natural drugs. Traditional Chinese medicine plays an important role in preventing and treating ALD. For example, *Panax Notoginseng* has attracted wide attention from researchers. Among these, the role of 4-hydroxynonenal (4-HNE) in the development of ALD, the relationship between intestinal flora and ALD, and functional foods with antioxidant effects are of great interest. The beneficial effects and targeted therapy of homologous drugs and functional foods in the treatment of ALD should be the trend of future research. This study provides an objective description of LPO in ALD and guidance for future scientific research.

Keywords: alcoholic liver disease; lipid peroxidation; bibliometric analysis; medicine and food homology; intestinal flora

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1 Introduction

Excessive alcohol consumption is an addictive behavior disorder[1]. In many individuals, consistently high levels of alcohol intake lead to alcoholic liver disease (ALD), which is one of the main causes of death worldwide[2]. Lipid peroxidation (LPO) is generally described as a process in which oxidants, such as free radicals, attack lipids containing carbon-carbon double bond(s), especially polyunsaturated fatty acids (PUFAs)[3]. LPO has been shown to be involved in a wide range of diseases, including metabolic diseases[4], neurodegenerative disorders[5], diabetes[6], atherosclerosis, and chronic inflammation[7] and so on. Excessive accumulation of free radicals and attack by reactive oxygen species (ROS) leads to LPO, and alcohol abuse is an important trigger for the development of this pathological state[8,9]. LPO and its products have been proved to play a significant role in the pathogenesis of ALD[10-13]. The Chinese people have a long history of drinking. Traditional Chinese medicine (TCM) has been widely used in the prevention and treatment of ALD to maintain health and reduce the occurrence of diseases. Homologous drugs in medicine and food play an important role[14,15]. With the development of science and technology, the mechanistic role of TCM in ALD treatment has received increasing attention. However, a research of modern medicine and TCM has not been systematically combed before.

Bibliometric[16,17] is an effective method commonly used to study the development of a field and predict future research hotspots. In this study, we collected data from the Web of Science Core Collection (WOSCC, an internationally recognized database reflecting the level of scientific research) and the China National Knowledge Infrastructure (CNKI, the most authoritative knowledge resource database of the whole society in China) over the past 20 years. We used the R-based Bibliometrix package[18], VOSviewer[19] and CiteSpace[20] to ensure a comprehensive study. The history, knowledge structure, research hotspots, and potential trends were then scientifically measured and systematically compared. The literature screening and visualization process used in this study is shown in Fig. 1.

2 Materials and methods

2.1 Data sources and search strategies

The literature was extracted from the WOSCC and downloaded

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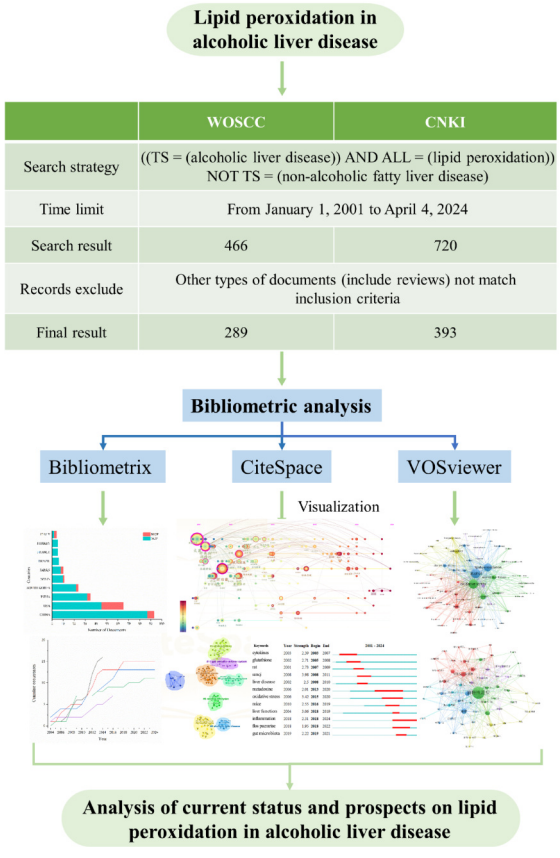

Figure 1 Literature screening and visualization process.

within one day on April 4, 2024. The search terms were as follows: ((TS = (alcoholic liver disease)) AND ALL = (lipid peroxidation)) NOT TS = (non-alcoholic fatty liver disease). The publication dates of the search were January 1, 2001, to April 4, 2024, resulting in 466 records. Only the research content mainly ALD, which is related to LPO was included. Reviews, meeting abstracts, newspaper articles, and published papers were excluded. Two reviewers independently carried out the literature processing process, and if the results of the arrangement were inconsistent, a third reviewer participated in the work. Finally, 289 articles were screened. The retrieved papers were further exported and saved as plain text files and stored in download_txt format.

A total of 720 Chinese articles were extracted from the CNKI database using the same retrieval strategy. A total of 393 papers were exported and saved in the refwork format.

2.2 Data analysis

In this study, the Bibliometrix 4.1.3 Package (https://www.bibliometrix.org) based on the R language, VOSviewer (version 1.6.18), and CiteSpace (version 6.3.R1) were used to perform a bibliometric analysis[21]. The relevant results of the CNKI analysis were translated for ease of reading.

3 Results

3.1 The trend of publication outputs and core journals

The number of publications in a specific period reflects the developmental trends of research in a field[22]. In the WOSCC, none of the papers were published between 2001–2004. Sixteen studies were published in 2004. Based on previous studies on the mechanism of ALD, foreign scholars began to focus their research on LPO in oxidative stress from 2004, and to carry out follow-up studies on its mechanism of action and treatment methods. From 2004 to 2024, the number of published studies fluctuated (Fig. 2). The number of published papers decreased from 21 in 2012 to 6 in 2019, which was the lowest. Subsequently, the number of

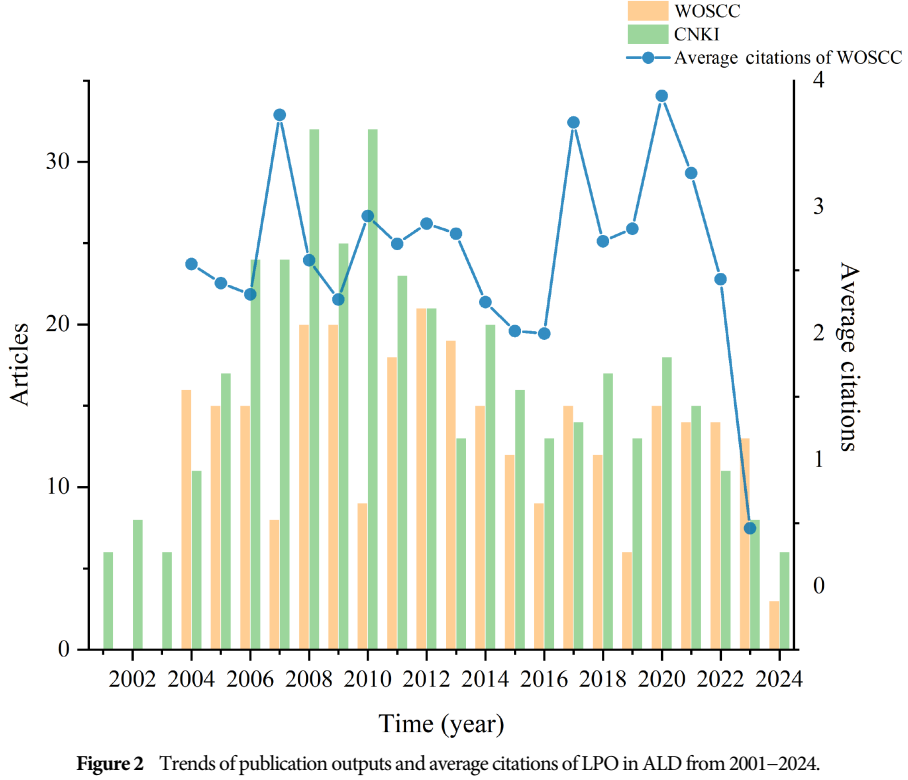

Figure 2 Trends of publication outputs and average citations of LPO in ALD from 2001–2024.

published papers increased slightly in the following two years. LPO in ALD has been adequately studied between 2008—2014. The results of CNKI showed trends similar to those of WOSCC. A fluctuating trend in the number of published articles has been observed in China. The highest number of publications was reached in 2008 and 2010 at 32.

Meanwhile, we noticed that over the past 20 years, the average number of citations per year in the WOSCC was less consistent with the changes in the number of articles issued. The top two average citations, 2007 and 2020, were both years with a low number of annual publications during the period. It is speculated that a possible reason for this is that the number of references available increases as research progresses and develops[23]. Therefore, the average number of citations in the literature was higher, even in years when the number of publications was low.

All articles on LPO in ALD were published in 131 journals of the WOSCC. The top 10 journals with the highest productivity are listed in Table 1. Approximately 31.8% of articles were published in these journals. *Food and Chemical Toxicology* (16 articles, cited 115 times) was the most prolific English journal. *Hepatology* was the most cited journal (6 articles, cited 838 times). The number of articles published in these journals from 2004 to 2024 showed an increasing trend year by year. From 2014 to now, *Food and Chemical Toxicology* ranked first, with 16 articles published annually (Fig. 3A). Further reading of the 16 papers revealed that nearly three-quarters of the papers were on natural plant extracts, the pharmacological mechanisms of which were mostly antioxidant, inhibition of mitochondrial oxidative stress, and anti-inflammatory. It is evident that plant extracts with green and safe characteristics are of great interest for the treatment of ALD (Fig. 3C). Three-field plots can be used to comprehensively analyze the relationship between different bibliometric indicators and build a comprehensive network map between indicators. Using three-fields plot analysis in the Bibliometrix package, select "author" on the left, "source" in the middle, and "keywords" in the right field to draw the network relationship between author, keyword and source (Fig. 3B). In *Food and Chemical Toxicology*, for example, published papers have focused on "oxidative stress" "lipid peroxidation" "alcoholic liver disease". The research topics of Petersen DR, who published the most, also focused on these topics. The top 10 journals with the highest productivity in CNKI include *Journal of Practical Hepatology*, *Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases*, *Shandong Medical Journal* and so forth (Table 2).

Table 1 Top 10 journals with the most publications in WOSCC

Rank	Source	Articles	Local citations	H-index	Impact factor (2023)
1	*Food and Chemical Toxicology*	16	115	15	3.9
2	*Alcoholism-Clinical and Experimental Research*	15	572	10	3.2
3	*Alcohol and Alcoholism*	13	151	11	2.1
4	*Free Radical Biology and Medicine*	11	405	10	7.1
5	*American Journal of Physiology-Gastrointestinal and Liver Physiology*	7	179	7	3.9
6	*Food & Function*	6	45	6	5.1
7	*Hepatology*	6	838	6	12.9
8	*Journal of Ethnopharmacology*	6	86	4	4.8
9	*Journal of Functional Foods*	6	36	5	3.8
10	*Journal of Hepatology*	6	315	6	26.8

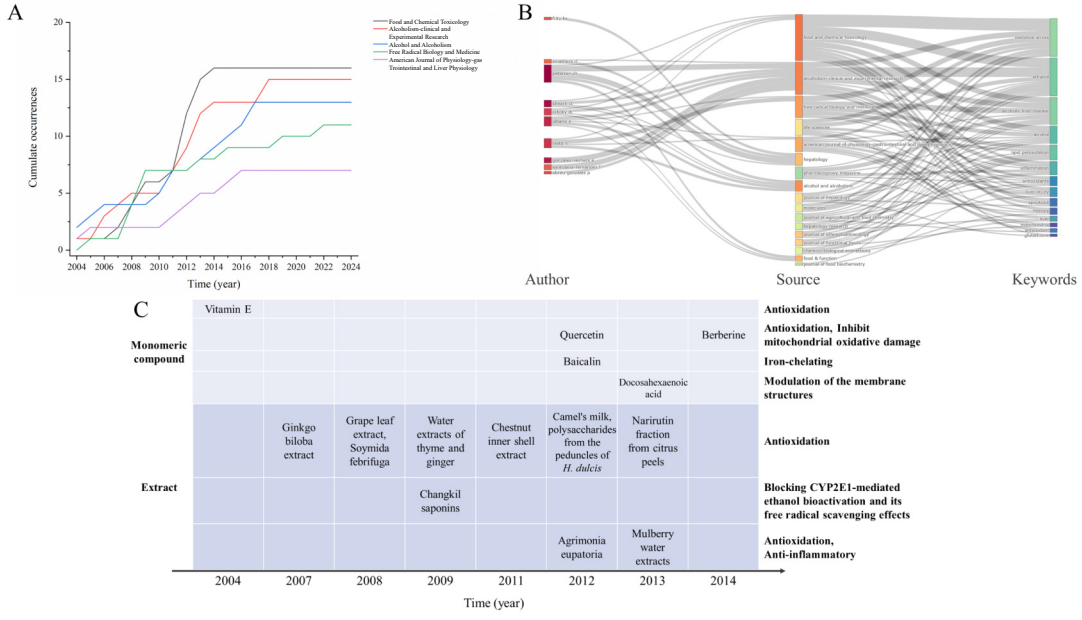

Figure 3 Top 10 journals and three-fields plot analysis. (A) Source dynamics of English literature, (B) Network relationship between authors, keywords and sources of English literature, (C) Analysis of the time of publication of *Food and Chemical Toxicology*, research subjects and research content.

Table 2 Top 10 journals with the most publications in CNKI

Rank	Sources	Articles
1	*Journal of Practical Hepatology*	15
2	*Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases*	14
3	*Shandong Medical Journal*	7
4	*China Practical Medicine*	7
5	*Guide of China Medicine*	7
6	*Chinese Archives of Traditional Chinese Medicine*	7
7	*Journal of Clinical Hepatology*	6
8	*Journal of China Medical University*	6
9	*Lishizhen Medicine and Materia Medica Research*	5
10	*Chinese Journal of Hepatology*	5

3.2 Profiling of countries/regions, institutions and active authors

In general, studies of highly productive countries in a field are useful for objectively evaluating the disciplinary influence of countries and institutions and for providing more references for subsequent scholarly research[24]. The results of the Bibliometrix package showed that the number of published papers in China, USA, and South Korea were the top three all over the world, with 66% of publications (Fig. 4A). The number of publications in the China and USA were 282 and 233, respectively, and the total number of citations was more than 2,500 (Table 3). However, it is not always proportional to the number of countries' publications and citations; for example, the number of publications in South Korea and India was very similar, while India's citations were almost twice as many as South Korea's. These results suggest that the influence and attention of research results in South Korea are basic, and the precision, breadth, and depth of academic research still have a lot of space to explore and develop, further improve academic value, and expand academic influence.

We analyzed the cooperation networks across countries (Fig. 4B) and corresponding author's country (Fig. 4C) simultaneously. Multiple country publications (MCP) represent the number of papers co-authored with authors from different countries, while single country publications (SCP) represent the number of papers co-authored with authors from the same country[25]. These results suggest that most countries only carry out academic cooperation at home, while international exchanges and cooperation are relatively scarce, and the number of MCP was less than one-third of the total number. Fig. 4D shows that nearly one-third of the publications came from University of Colorado Anschutz Medical Campus, Rhode Island Hospital, University of Colorado system, and Brown University, and they all attached to USA.

The H-index refers to the fact that N of all academic papers published by an individual is cited at least N times each[26]. Compared to the total impact factor and total citations alone, the H-index is considered both the quantity and quality of a researcher's academic output. The top 10 productive authors of the WOSCC are listed in Table 4. They contributed to 82 publications, accounting for 28.4% of the total number of papers. Petersen DR from the University of Colorado Health Sciences Center was first placed in the field of LPO in ALD, followed by Shearn CT and González-Reimers E. By browsing published papers on Petersen DR, we found that he became concerned with the pathological mechanisms associated with ALD in 1976. Initially, he focused on the effects of ethanol consumption on hepatic microsomes. In 1982, he studied the

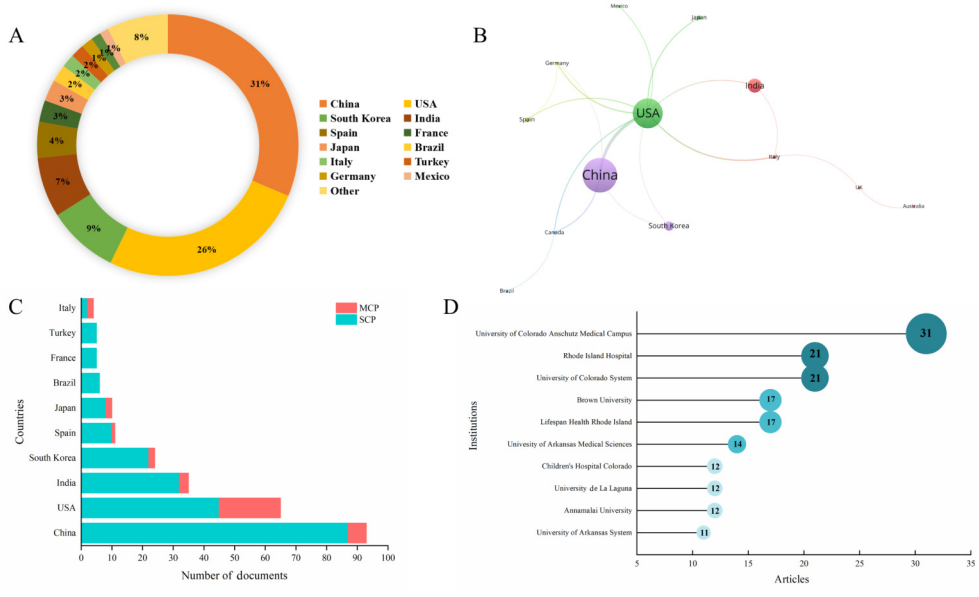

Figure 4 Visualization of countries and institutions analysis. (A) Proportional distribution of global outputs, (B) Cooperation networks across countries, (C) Corresponding author's country, (D) Articles for the top 10 institutions.

Table 3 Articles and total citations for the top 10 producing countries

Rank	Countries	Articles	Total citations
1	China	282	2,551
2	USA	233	3,011
3	South Korea	79	398
4	India	67	1,009
5	Spain	40	156
6	France	24	156
7	Japan	24	286
8	Brazil	19	100
9	Italy	15	88
10	Turkey	15	108

Table 4 Top 10 authors with the most publications

Rank	Author	Country	Articles	Total citations	H-index
1	Petersen DR	USA	19	86	17
2	Shearn CT	USA	10	32	9
3	González-Reimers E	Spain	8	2	6
4	Albano E	Italy	7	23	7
5	Nieto N	USA	7	8	7
6	Orlicky DJ	USA	7	18	7
7	Abreu-González P	Spain	6	1	5
8	Fritz KS	USA	6	26	6
9	Santolaria-Fernández F	Spain	6	2	6
10	Smathers RL	USA	6	27	6

molecular mechanisms associated with LPO in ALD, including the modification of proteins by LPO products, such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA).

Figure 5A shows the timeline distribution of the top 10 most productive authors and the cooperation authors' network. The node size indicates the number of publications. The colors of the nodes were light to dark blue, indicating that the number of citations were small to large. Within the search range, Petersen DR is an early researcher on LPO in ALD. Thus far, he has been engaged in research in this field for 15 years (2004–2018). Using VOSviewer (Figs. 5B and 5C), the co-authorship network in WOSCC shows that only 7 authors showed a close cooperative relationship, and Petersen DR was at its heart. The degree of cooperation among the authors was relatively low and was characterized by cooperation within the country.

In CNKI, 20 authors had a collaborative relationship and could be divided into five clusters. Zhi-Yun Chen, Bing-Yuan Wang, and Bao-Yu Fu were the core authors. Among them, the research team represented by Zhi-Yun Chen, conducted a comprehensive and detailed study on the mechanism of action of *Notoginseng Radix et Rhizoma* in the treatment of ALD, including its effects on oxidative stress factors, inflammatory factors, and related protein expression in ALD rats. The team mainly conducted research on digestive diseases, including chronic atrophic gastritis and irritable bowel syndrome. Unfortunately, the team's research on ALD was only published between 2008–2011, after which the research direction shifted to NAFLD and liver fibrosis.

3.3 Analysis of documents

A literature citation and co-citation analysis of English literature was conducted[27,28]. Local citation scores (LCS) is the most locally cited document, which means highly cited literature in the current dataset, and global citation scores (GCS) is the most globally cited document, which means highly cited literature in the WOSCC[29]. If a document has a high GCS but not a high LCS, this probably means that it has a greater impact in other fields. Co-citation analysis refers to the co-citation relationship formed when two articles appear together in the bibliography of a third-cited article. The number of co-citations is used to measure the similarity between the two documents. It was completed using CiteSpace.

The top 15 highest contributions to the dataset include 12 pieces from 2004 to 2010 and 3 pieces from 2011 to 2013 (Table 5). Most articles focused on the pathogenesis of ALD, especially some important factors such as 4-HNE, and the mechanism of action of drugs used to treat ALD, such as anti-oxidation and reducing LPO. The most cited article was written by Carbone DL, who reported that HSP 90 was modified by 4-HNE in a rat model of chronic ALD (LCS 9, GCS 145)[30]. Subsequently, Galligan *et al.*[31] (LCS 5, GCS 58) confirmed the

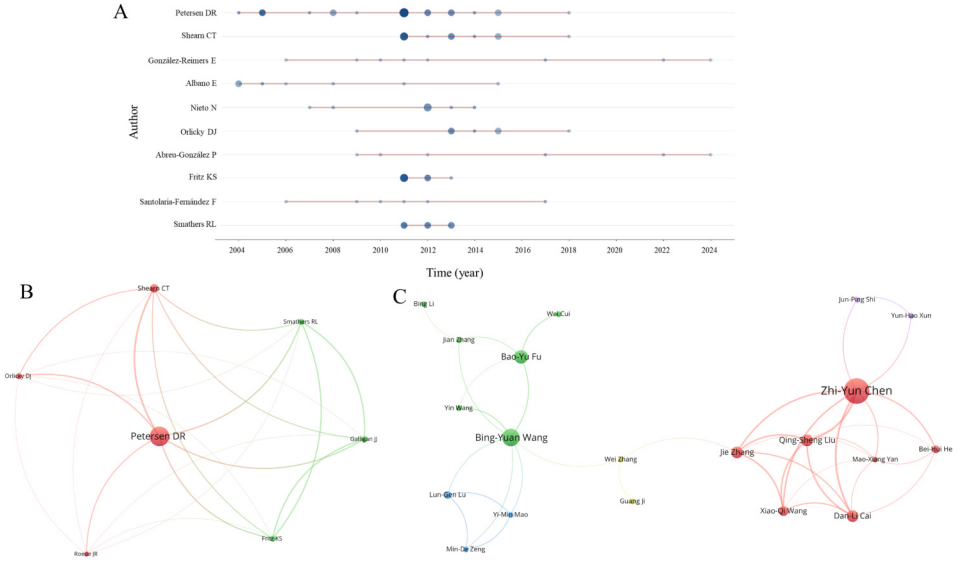

Figure 5 Visualization of active authors analysis. (A) Timeline distribution of the top 10 most productive authors, (B) Cluster analysis of cooperation among authors in WOSCC, (C) Cluster analysis of cooperation among authors in CNKI.

Table 5 Top 15 cited English literature

No.	Title	DOI	Time (year)	LCS	GCS
1	*Modification of heat shock protein 90 by 4-hydroxynonenal in a rat model of chronic alcoholic liver disease*	http//:doi.org/10.1124/jpet.105.088088	2005	9	145
2	*Effects of N-acetylcysteine on ethanol-induced hepatotoxicity in rats fed via total enteral nutrition*	http//:doi.org/10.1016/j.freeradbiomed.2005.04.011	2005	9	92
3	*Silymarin protects against acute ethanol-induced hepatotoxicity in mice*	http//:doi.org/10.1111/j.1530-0277.2006.00063.x	2006	9	124
4	*Decreased expression of peroxiredoxin 6 in a mouse model of ethanol consumption*	http//:doi.org/10.1016/j.freeradbiomed.2008.08.032	2008	7	36
5	*Prevention of alcoholic fatty liver and mitochondrial dysfunction in the rat by long-chain polyunsaturated fatty acids*	http//:doi.org/10.1016/j.jhep.2008.04.023	2008	7	87
6	*4-Hydroxynonenal inhibits SIRT3 via thiol-specific modification*	http//:doi.org/10.1021/tx100355a	2011	7	97
7	*Inhibition of Hsp72-mediated protein refolding by 4-hydroxy-2-nonenal*	http//:doi.org/10.1021/tx049838g	2004	6	95
8	*Oxidative stress as a trigger for cellular immune responses in patients with alcoholic liver disease*	http//:doi.org/10.1002/hep.20021	2004	6	72
9	*Ethanol-induced modulation of hepatocellular extracellular signal-regulated kinase-1/2 activity via 4-hydroxynonenal*	http//:doi.org/10.1074/jbc.M610602200	2007	6	53
10	*In vitro and in silico characterization of peroxiredoxin 6 modified by 4-hydroxynonenal and 4-oxononenal*	http//:doi.org/10.1021/tx800244u	2008	6	42
11	*Protective effect of bicyclol on acute alcohol-induced liver injury in mice*	http//:doi.org/10.1016/j.ejphar.2008.02.059	2008	6	71
12	*Oxidative stress and antioxidant status in patients with alcoholic liver disease*	http//:doi.org/10.1016/j.cccn.2004.12.012	2005	5	64
13	*Protective effect of ursolic acid on ethanol-mediated experimental liver damage in rats*	http//:doi.org/10.1016/j.lfs.2005.05.060	2006	5	148
14	*Preliminary characterization, antioxidant activity in vitro and hepatoprotective effect on acute alcohol-induced liver injury in mice of polysaccharides from the peduncles of Hovenia dulcis*	http//:doi.org/10.1016/j.fct.2012.06.034	2012	5	129
15	*Protein carbonylation in a murine model for early alcoholic liver disease*	http//:doi.org/10.1021/tx300002q	2012	5	58

presence of a novel protein modification site for 4-HNE *in vivo*. Besides, Shearn *et al.*[32] (LCS 4, GCS 39) noticed 4-HNE mediated inhibition of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) contributed to the observed activation of Akt2, suggesting a possible new mechanism for lipid accumulation due to the increased production of reactive aldehydes during chronic ethanol administration in mice.

We subsequently constructed a visualization network of co-citation references and performed cluster analysis based on the latent semantic indexing (LSI) algorithm (Fig. 6). A total of 8 clusters were found; the modularity *Q* was 0.849,1, and the mean silhouette value was 0.951,5, showing significant and convincing cluster results[33]. The first three clusters were "#1 Oxidative stress" "#2 Kupffer cells" "#3 Ethanol feeding". During the LPO in the ALD study, common study methods, and categories of findings were included in the three clusters.

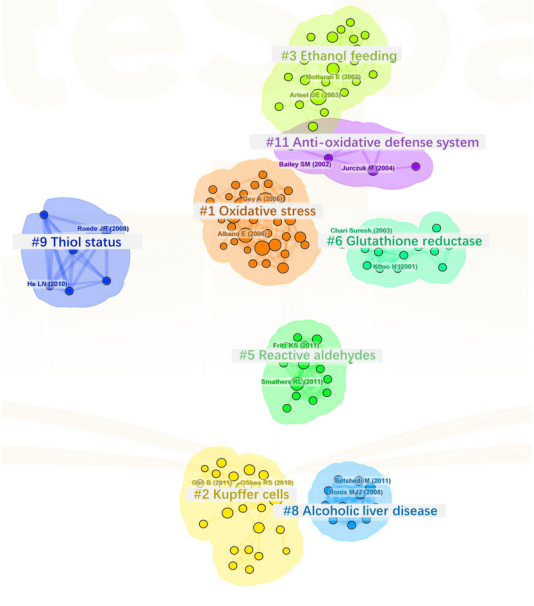

Figure 6 Co-citation analysis network of English reference.

The highly cited literature was read and analyzed in depth to map ethanol metabolism and cellular injury in the pathogenesis of ALD (Fig. 7). ALD includes steatosis, liver fibrosis, alcoholic hepatitis, and cirrhosis. During the course of the disease, the metabolic process of ethanol intake into the body leads to the accumulation of ROS, mainly H_2O_2 and O^{2-}, which rapidly bind to ethanol or iron atoms to form reactive metabolites, such as hydroxyl radicals (·OH), ferrous oxide (FeO), or hydroxyethyl radicals (CH_3CHOH), which are responsible for cell membrane LPO[9]. In addition, mitochondria (through the respiratory chain), endoplasmic reticulum (through CYP2E1), and Kupffer cells (through NADPH oxidase) are the main sources of ROS, leading to the development of oxidative stress. 4-HNE, one of the most important LPO products, is of great interest to researchers because of its production process and the mechanisms affecting the disease process[11,34]. A study by Smathers *et al.*[35] indicated that 4-HNE modifies essential cellular proteins, resulting in the loss of protein function and cellular homeostasis. Hepatic proteins that are modified by 4-HNE include heat shock protein 70 (Hsp70), Hsp90, protein disulfide isomerase (PDI), extracellular signal-regulated kinase-1/2 (Erk1/2), peroxiredoxin 6 (Prx6) and liver fatty acid-binding protein (L-FABP), etc.

3.4 Analysis of keywords

Keyword co-occurrence refers to the co-occurrence of two or more keywords in the same paper, which can show the relationship and structure of these keywords in the research field, reveal the research development trend, and facilitate the discovery of new disciplinary growth points and trends[36]. The VOSviewer software was used to cluster the keywords. The circle and label form an element, the color of which identifies the cluster to which it belongs. In WOSCC (Fig. 8A), "alcohol" (160), "oxidative

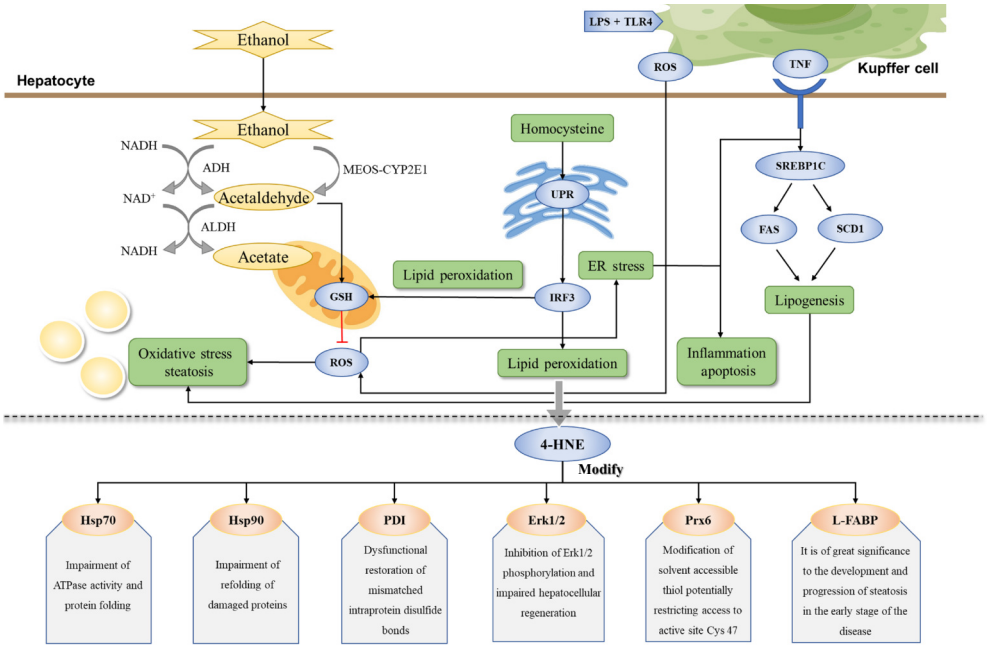

Figure 7 Metabolism of ethanol and related cell injury, 4-HNE and its hepatic protein modification in ALD.

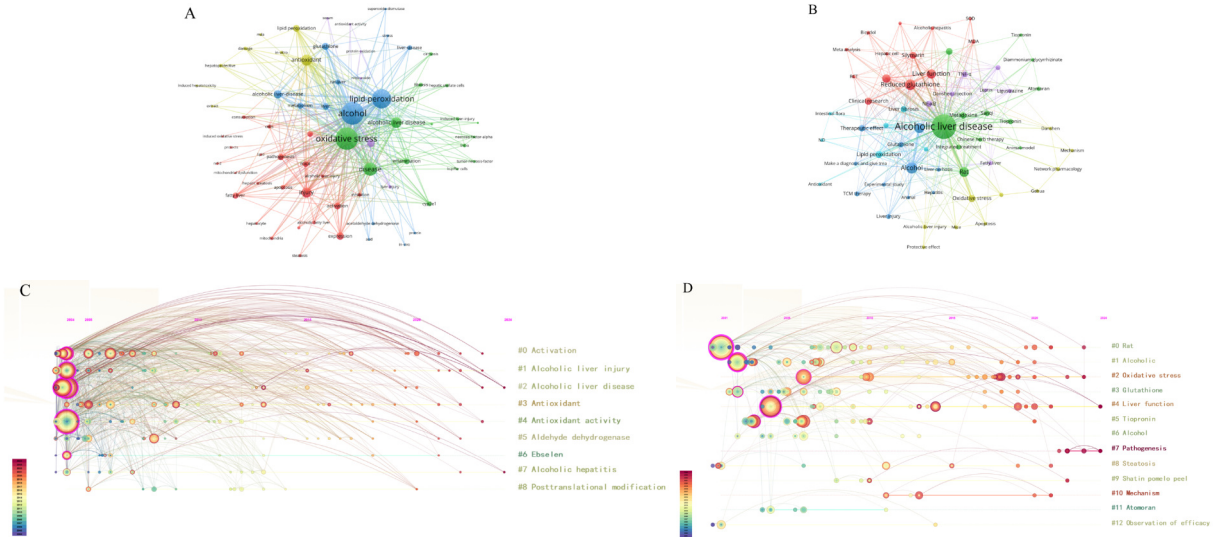

Figure 8 Visualization map of keywords clustering analysis. (A) Keywords in WOSCC, (B) Keywords in CNKI, (C) The timeline map of clustering analysis of keywords in WOSCC, (D) The timeline map of clustering analysis of keywords in CNKI.

stress" (158) and "lipid-peroxidation" (132) were the cure keywords. The blue and green cluster represented the basic concepts related to LPO and ALD, including "lipid peroxidation" "inflammation" and "alcoholic hepatitis", they also indicate pathological process changes in ALD, including "mitochondrial dysfunction" "steatosis" and "fibrosis". The red, yellow and purple cluster were related to the pathogenesis of ALD, including some important factors such as Nrf-2, and the effect of mitochondria and reactive oxygen at the same time, rats were usually used for ALD. In CNKI (Fig. 8B), "alcoholic liver disease" was the most frequent occurrence, reaching 288 times. The red cluster is a series of clinical studies and meta-analysis on reduced glutathione (GSH). The blue, cyan, and yellow clusters include various methods and methods for studying the mechanism and treatment of ALD, such as "gut microbiota" "network pharmacology" and "apoptosis". The purple cluster showed that TCM and TCM combine with western medicine usually used to treat ALD, such as "Danshen injection" and "Chuanxiongzin". Besides, "liver clearing and blood activation formula" and "Zhige oral liquid" were prescriptions with a lot of research.

The clustering analysis based on the log-likelihood ratio (LLR) test algorithm was performed for the keywords in WOSCC and CNKI, and the timeline of the clusters was plotted by selecting "timeline". The horizontal coordinate (x) of the timeline view is the year of publication and the vertical coordinate (y) is the cluster number. A longer time span represents an earlier and more continuous field of study in the cluster. As shown in Figs. 8C and 8D, the research areas represented by "#0 Activation" "#2 Alcoholic liver disease" and "#7 Alcoholic hepatitis" had a relatively long-time span and were ongoing research hotspots in WOSCC. Meanwhile, CNKI shows that "#4 Liver function" and "#7 Pathogenesis" were primary research hotspots that were followed with interest by Chinese researchers.

Keyword emergence refers to a significant increase in the

frequency of a term within a short period of time, indicating that research in the field has received much attention from researchers during a certain period[37]. It can determine cutting-edge progress and research trends in the field. The start and end times of the mutation are indicated by "begin" and "end", respectively, and "strength" is the keyword mutation strength. The higher the strength, the greater is the influence. In keyword emergence, the light blue part represents the time span of the included literature and the red part represents the beginning and end of a keyword outbreak. In WOSCC (Fig. 9A), the top five in terms of prominence were liver disease, serum, free radicals, hepatic stellate cells, and *in vitro*. For the duration of the study, research hotspots focused on *in vitro* efficacy tests before 2010. Since 2010, with the deepening of research, mice have been used to elucidate the pathogenesis in quality, and the pathogenesis of ALD was studied in more depth. In CNKI (Fig. 9B), the top five in terms of prominence were cytokines, GSH, rat, Sanqi, and liver disease. For the duration of the study, the clinical efficacy of the drugs is an ongoing concern. From 2001 to 2011, Chinese researchers focused more on the medical treatment of ALD, including TCM, such as Sanqi (*Notoginseng Radix* et *Rhizoma*), and other drugs, such as GSH. During 2011–2022, researchers focused on the mechanism of action of drugs, and oxidative stress was a major contributor.

4 Discussion and conclusion

4.1 Current status of LPO in ALD

A visual analysis of country and institutional publication outputs through the Bibliometrix package in the R language environment shows that the number of domestic and international publication outputs concentrated on outbreak in 2008–2014. During this stage, researchers have gained a deep and comprehensive understanding of the pathogenesis and development of ALD. China and USA have been working on pathogenesis, treatment strategies, and preventive measures for ALD, they are way ahead of other countries in the number of published articles. Although countries possess cooperation networks, the breadth and intensity of cooperation are not ideal. As for research institutions, most cooperating institutions are limited to internal connections, and there are substantially less transnational cooperation and exchange of findings. This hinders the development of LPO in ALD. Therefore, it is strongly suggested that countries remove academic barriers, cooperate, and communicate to promote the research and development of LPO in ALD.

ALD cannot be induced and developed without long-term alcohol intake. Quitting drinking is not an easy task; therefore, people would like to find some daily health care measures against ALD[38]. This probably explains why three of the top 10 cited journals are in the food category. TCM theory has played an important role in the treatment of alcohol-related diseases over thousands of years of use, and is now gradually gaining more attention from scholars worldwide[39,40]. TCM has unique advantages in the treatment of ALD because most traditional herbs are medicinal and food based. Chinese scholars are working to deliver the culture of TCM to the world in a scientific manner to help the global treatment of ALD.

The act of citing other papers in a thesis is the flow of knowledge from different research topics to the research currently being conducted, and the process of reorganizing knowledge units from a state of straying to the generation of new knowledge[41]. We have summarized the important turning points in the publication of literature on WOSCC and CNKI, as shown in Fig. 10. Interestingly, international and Chinese studies show the opposite research history. International research begins with the pathogenesis of ALD and then selects single compounds or extracts for therapeutic or preventive studies based on its pathogenesis. TCM is an empirical science that has been used for thousands of years. In the early stages of use, doctors judged whether the drugs were effective solely based on clinical presentation, which provided valuable application experience in the use of Chinese medicine. Therefore, Chinese scholars first focus on the clinical efficacy of relevant therapeutic prescriptions and then delve into their specific mechanisms of action in ALD. As TCM has multiple components, Chinese scholars have focused their research on identifying the active ingredients and exploring multiple therapeutic pathways and targets of the herbs. Therefore, the difference between global and Chinese research history is not difficult to understand.

4.2 Future outlook in the LPO in ALD

4.2.1 *The molecular mechanism of LPO in ALD*

In previous research, scholars' exploration of the pathogenesis of LPO in ALD has focused on LPO products and fatty acids. Smathers *et al.*[35] identified hepatic proteins that are targets of 4-HNE modification and determined their relationship to the

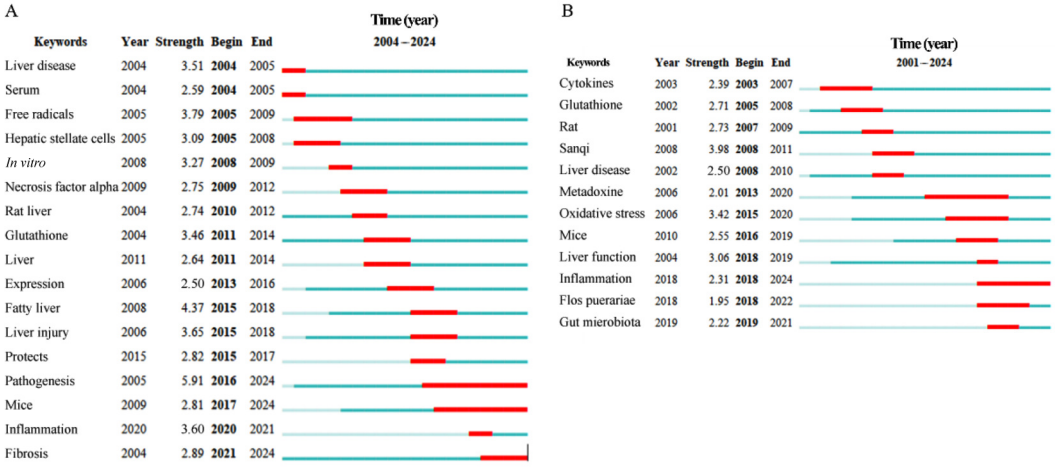

Figure 9 Emergence of keywords. (A) Emergence of keywords in WOSCC, (B) Emergence of keywords in CNKI.

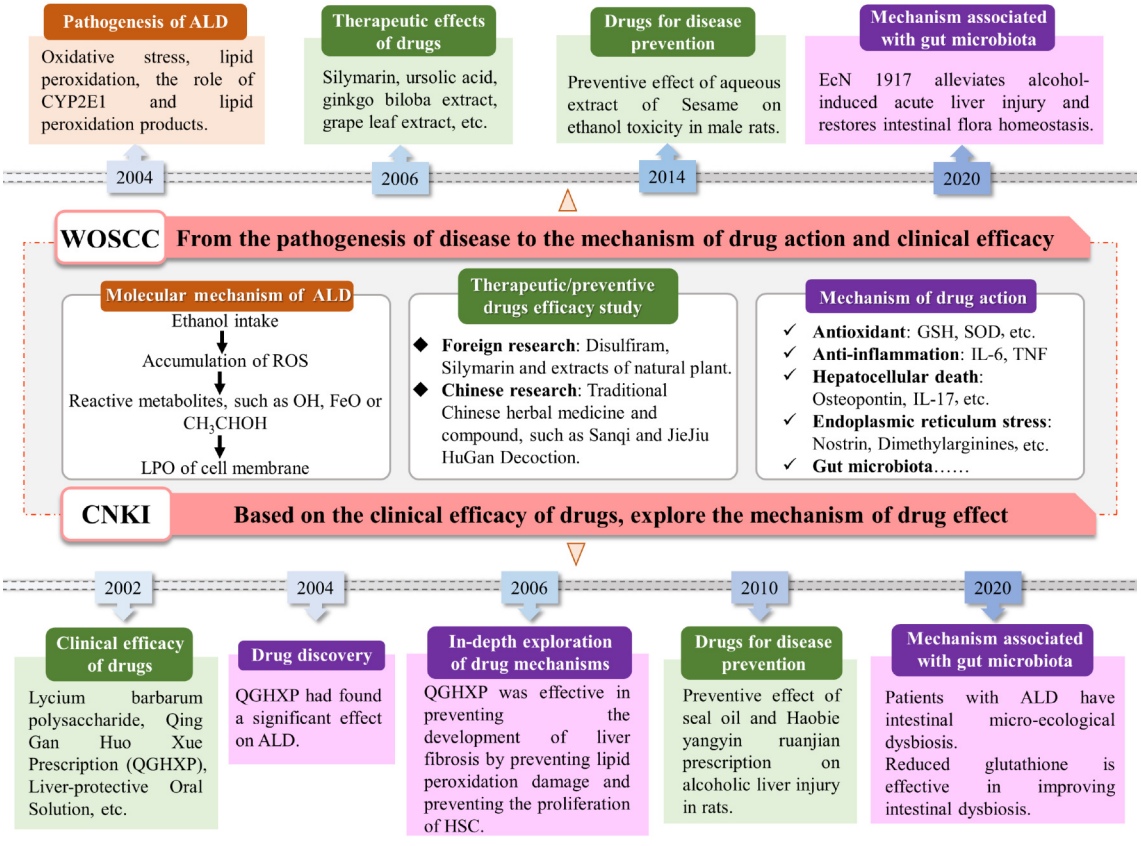

Figure 10 Global and Chinese study structure and history of LPO in ALD.

progression of the early stages of ALD. Song *et al.*[42] experimentally verified that the addition of DHA (docosahexaenoic)/AA (arachidonic) to the animal diet prevents alcohol-induced fatty liver and mitochondrial dysfunction by protecting various mitochondrial enzymes, most likely by reducing oxidative/nitrosation stress. In addition, Bridle *et al.*[43] found that downregulation of iron-regulated and *C/EBPα* gene expression implies a disruption of iron sensing, leading to hepatosiderosis in ALD, possibly through a mechanism involving the interleukin-6 (IL-6) signaling cascade.

Furthermore, with the introduction of the gut-liver axis, early discoveries in ALD identified increased levels of bacterial endotoxins in the portal circulation. Indeed, alcohol consumption can disrupt the intestinal epithelial barrier and result in increased gut permeability, which is increasingly being recognized as a major factor in ALD. Bacterial endotoxins are prototypic microbe-derived inflammatory signals that contribute to inflammation in ALD through activation of Toll-like receptor 4 (TLR4). In recent years, researchers have attempted to explore the possible mechanisms of drug treatment for ALD from the perspective of regulating intestinal flora, which will also be a hot spot for research in the coming period.

4.2.2 *The preventive and treatment for ALD*

Relevant antioxidants and anti-inflammatory agents have been studied by foreign scholars. These studies included drugs commonly used in clinical treatment, monomeric compounds, and plant extracts. For example, silymarin and dicyclol[44,45]. Natural plants have received considerable attention from researchers because of their safety. The efficacy and mechanism of action of extracts of ursolic acid[46], grape leaves[47], linum usitatissimum[48] and others in the treatment of ALD have been investigated by foreign scholars. Further definition of their potent substances and evaluation of their drug-forming properties will be a hot topic for future research. Additionally, by restoring the normal ecology of the intestinal flora and reshaping its balance of the intestinal flora, drugs can trigger a series of positive regulations in the body to achieve disease treatment. Drug development targeting intestinal flora is a feasible research direction for the future.

Early Chinese studies focused on the clinical efficacy of drugs and principles. The concept of "treating the disease before it occurs" in TCM is in line with the modern scientific concept of preventive healthcare. TCM contains herbs that are both medicinal and food, which provides a good basis for the prevention and treatment of ALD. In the theory of TCM, the cause of ALD is the existence of damp-heat and evil Qi in the body, resulting in the imbalance of the rise and fall of Qi machinery of Zangfu organs, which is divided into syndrome types such as damp-heat accumulation and stagnation of heat in the liver and stomach. The syndrome belongs to the stagnation of heat in the liver and stomach, the treatment should be soothing the liver and reducing the fire, and the stomach pain, with Danggui (*Angelicae sinensis radix*), Huanglian (*Coptidis rhizoma*), Sanqi[49], JieJiu HuGan Decoction[50], and Qinggan Huoxue Decoction[51], etc. Syndrome belongs to dampness and heat accumulation, treatment should clear the dampness and heat, with Chaihu (*Bupleuri Radix*)[52], Haobie Yangyin Ruanjian Decoction[53], etc. Such studies have visually demonstrated the effectiveness of TCM compounding; however, its material basis and mechanism of action have not yet been elucidated. After 2007, experimental animal models were used to evaluate the efficacy of

gradually increasing prescribed prescriptions. Owing to the multi-component and multi-target characteristics of Chinese medicine, the mechanism of action of Chinese medicine prescriptions for the treatment of ALD is more complex than that of single plant extracts. Therefore, for Chinese scholars, elucidating the material basis of compound prescriptions and exploring their mechanisms of action will be the focus of research in this field.

We collected information on national and international research and built a knowledge base including the internal structure, hotspot evolution, and emerging themes of LPO research in ALD from 2001–2024. The combination of the Bibliometrix package, CiteSpace, and VOSviewer can complement each other to provide a more comprehensive and complete picture of research in the field. The China and USA are the main countries that focus on this issue. However, the collaboration and communication between countries and institutions must be strengthened. Most studies have focused on the role of 4-HNE in the pathogenesis of ALD and the drug action mechanism of targeted therapy of 4-HNE and its modified proteins. With the development of the gut-liver axis, the relationship between intestinal flora and ALD has also been extensively discussed, and drug development based on the regulation of intestinal flora is a feasible direction in the future.

Furthermore, control of alcohol intake and a healthy lifestyle are essential for the prevention and treatment of ALD, and dietary therapy is an important part of ALD treatment and prevention measures. Consequently, natural and safe traditional medicines, such as medicine and food homologous drugs in TCM, will play an important role in the treatment of ALD. By systematically collating and analyzing the current research, we have not only provided a reference for subsequent researchers, but also helped the world understand TCM.

Conflicts of interest

The authors declare no conflict of interest.

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