REVIEW ARTICLE

Molecular Regulatory Network and Therapeutic Potential of Ferroptosis in Gastric Cancer: An Exploration Combining Bibliometrics and Mechanistic Review

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Abstract

Gastric cancer, a prevalent malignancy of the digestive tract, continues to pose significant challenges in pathogenesis and prognosis improvement. Ferroptosis has emerged as a promising therapeutic breakthrough due to its critical role in inhibiting tumor growth and reversing drug resistance. This study employs bibliometric and visual analysis tools, utilizing the Web of Science database (up to October 20, 2025), to systematically analyze 362 English-language papers on ferroptosis in gastric cancer (GC), authored by 2,458 researchers across 16 countries and published in 189 journals. The analysis reveals a rapidly growing field, with 74.86% of papers published in the last three years, and identifies China, the USA, and Japan as leading contributors. Using VOSviewer and CiteSpace, the study maps publication trends, collaboration networks, and keyword co-occurrence, identifying core research hotspots centered on the molecular regulatory framework of ferroptosis. Meanwhile, we systematically summarize and comprehensively discuss the potential mechanisms of ferroptosis involved in GC occurrence and progression. By integrating bibliometric analysis with comprehensive review, this study clarifies the intrinsic relationship between gastric cancer and ferroptosis. Current efforts are focused on identifying and developing novel strategies to inhibit cancer proliferation and overcome drug resistance. By systematically outlining the knowledge structure, research evolution, and future directions of GC ferroptosis, this work provides a comprehensive foundation for researchers, fostering deeper insights and accelerating the translation of fundamental discoveries into clinical applications.

Keywords: gastric cancer, ferroptosis, molecular regulatory network, therapeutic potential, bibliometric

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analysis.

1 Introduction

Gastric Cancer (GC) is the fifth most prevalent malignant tumor and the fourth leading cause of cancer-related fatalities. This complex and highly diverse disease arises from primary epithelial cancers of the stomach and is influenced by numerous risk factors [1]. Over the last ten years, studies have shown a notable decrease in incidence rates in specific regions and demographic groups, while other areas report stable or increasing rates of GC. Concurrently, mechanistic research has advanced substantially; for instance, the pivotal role of Glutathione Peroxidase 4 (*GPX4*) in regulating ferroptotic cancer cell death has been established as a central determinant in tumor biology [2]. The highest incidence of GC is found in East Asia, Central and South America, and Eastern Europe, with males being more affected than females [3]. As one of the deadliest cancers, GC has a five-year survival rate of around 20% [4]. Various risk factors contribute to its development, with a strong link to *Helicobacter pylori* infection. Other factors include dietary choices, alcohol use, smoking, obesity, exposure to radiation, lack of physical activity, and high cholesterol levels [5–7]. Ferroptosis, a distinct form of iron-dependent regulated cell death [8], occurs when polyunsaturated fatty acyl tails in phospholipids are oxidized in an iron-dependent manner [9]. The underlying mechanisms involve disruptions in iron metabolism, lipid peroxidation, imbalances in iron homeostasis, redox disturbances, compromised antioxidant defenses, and the buildup of reactive oxygen species (ROS) [10–14]. Research indicates that ferroptosis plays a crucial role in various biological processes, particularly in the metabolism of iron, lipids, and amino acids [15]. Metabolic pathways within mitochondria, the endoplasmic reticulum, lipid droplets, peroxisomes, and other organelles are essential for modulating sensitivity to ferroptosis [16]. Findings suggest that drug-resistant cancer cells, particularly those in a mesenchymal state that increases their metastatic potential, show greater vulnerability to ferroptosis [17]. Studies have confirmed that several experimental agents (such as erastin and RSL3), certain drugs (including sorafenib, sulfasalazine, statins, and artemisinin), ionizing radiation, and cytokines (like Interferon-γ (IFN-γ) and Transforming Growth Factor-β1 (TGFβ1)) can effectively trigger ferroptosis and inhibit tumor growth [18]. This study performs a systematic bibliometric and visual analysis of research on ferroptosis in GC. From multiple perspectives including countries, institutions, journals, authors, references and keywords, we explored the correlations among relevant studies to highlight key contributors, institutions, nations and current research trends. Meanwhile, we systematically reviewed the underlying mechanisms of ferroptosis in the occurrence and progression of gastric cancer. By organically combining bibliometric analysis with mechanistic review, this paper further clarifies the relationship between gastric cancer and ferroptosis. The findings provide insights and directional guidance for future related research.

2 Materials and Methods

2.1 Data Collection

This research performed a comprehensive search within the Web of Science database, covering a period up to October 20, 2025. The keywords utilized were: TS=('Stomach Neoplasms' OR 'Stomach Neoplasm*' OR 'Gastric Neoplasm*' OR 'Stomach Cancer*' OR 'Gastric Cancer*' OR 'Gastric Tumor*' OR 'Stomach Tumor*' OR 'Stomach Carcinoma*' OR 'Gastric Carcinoma*') AND TS=('Ferroptosis' OR 'Oxytosis'). An initial search resulted in 544 articles. Following a thorough review to eliminate duplicates and unrelated content, 362 relevant publications were chosen for further examination. To maintain the integrity of the data, all literature details were standardized before the formal analysis, which involved harmonizing country names, institutional details, journal abbreviations, and conceptual terms. The process of selecting literature is depicted in Figure 1.

2.2 Inclusion and Exclusion Criteria

The objective of this research is to explore the link between ferroptosis and GC, utilizing a range of research approaches. We will focus exclusively on English-language studies that fulfill specific inclusion criteria: these must be research articles that offer detailed bibliographic details, such as the title, authors' nationalities and affiliations, names of researchers, relevant keywords, and the journal of publication. Accepted study types will include clinical trials, fundamental research, animal studies, data mining, and review articles. We will eliminate duplicate entries, literature that lacks significant relevance to the main topic, and any retracted papers to maintain the quality and pertinence of our review.

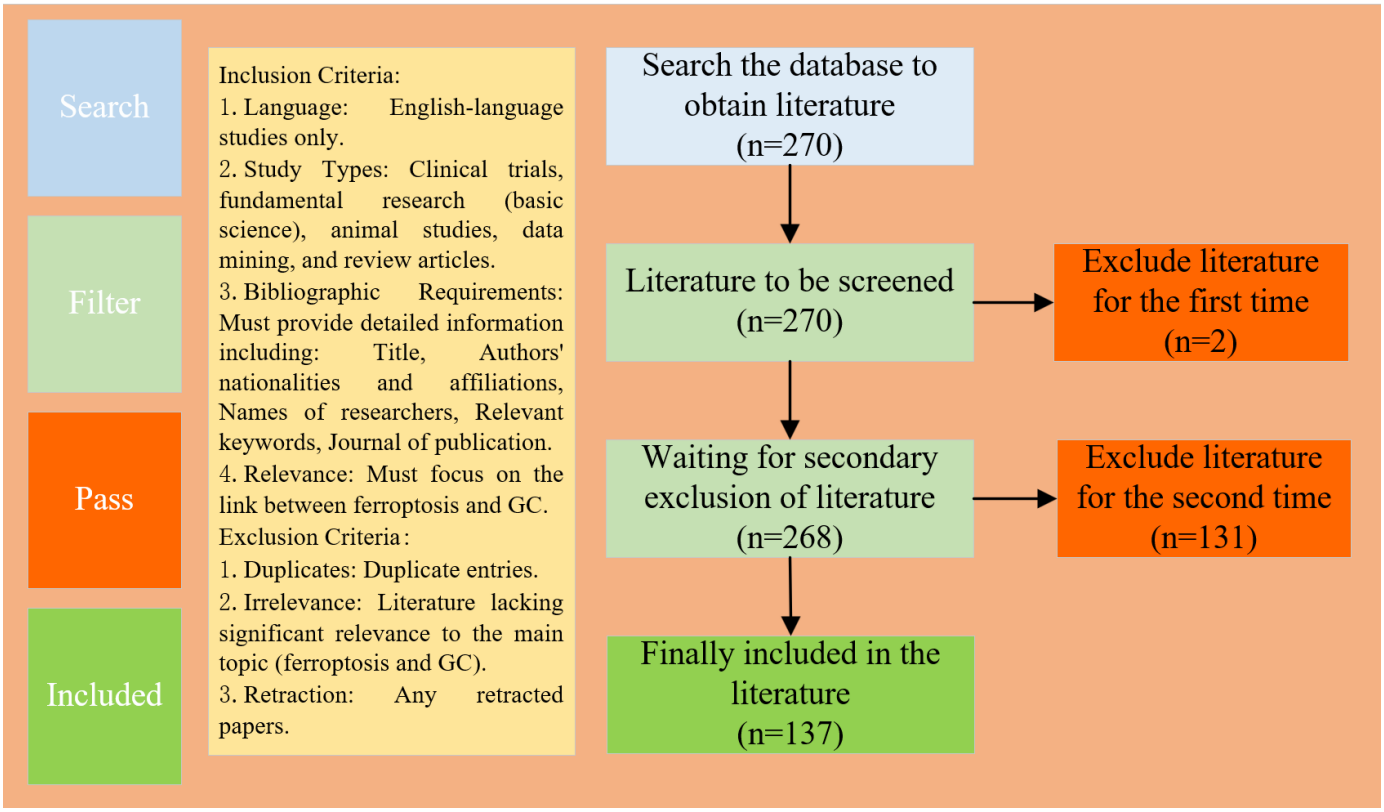

Figure 1. Literature screening process.

2.3 Analytical Tools and Methods

This research utilizes various tools, including VOSviewer 1.6.20, CiteSpace 6.4.R1 Advanced, the R Package biblioshiny, and Excel, to perform bibliometric and visual analyses. By processing data and creating visual representations, the research offers a comprehensive view of the field. It specifically investigates the contributions and collaborative networks among nations, authors, institutions, journals, references, and keywords. Additionally, it incorporates methods such as journal dual-map overlay analysis, timeline mapping, keyword clustering, and high-citation burst mapping to deliver an in-depth, multifaceted understanding of the research outcomes.

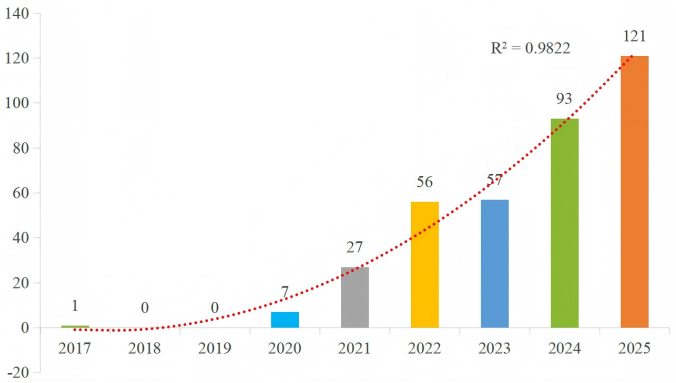

Figure 2. Annual publication volume and growth trend.

3 Results

3.1 Publication Analysis

A comprehensive analysis of 362 scholarly articles has identified unique phases in the output of research. As illustrated in Figure 2, the number of publications remained consistent at seven or fewer annually from 2017 to 2020. However, a remarkable surge in research began in 2021, with 27 papers published, marking a notable rise from earlier years. The following year saw an even more dramatic increase, with annual publications jumping to 56. This upward trend persisted, with 57 papers in 2023, followed by a significant rise to 93 in 2024, and reaching a record high of 121 in 2025. The statistical analysis shows a strong positive relationship between the yearly count of published papers and the corresponding year, evidenced by a correlation coefficient of 0.9822. This upward trajectory signifies a growing scholarly focus on ferroptosis in GC. Presently, researchers are investigating innovative strategies for the prevention and treatment of GC that leverage the mechanisms of ferroptosis, paving the way for advancements in this area.

3.2 National Analysis

Table 1. Top 10 countries with the highest number of publications.

Ranking	Countries	Number of Documents	Total Citations	Average Citations per Publication
1	China	346	7167	20.9
2	USA	17	52	26
3	Japan	5	64	12.8
4	South korea	4	361	120.3
5	Canada	3	0	0
6	Germany	3	12	6
7	Iran	2	2	1
8	Singapore	2	0	0
9	Turkiye	2	0	0
10	Denmark	1	8	8

A total of 16 nations worldwide have engaged in scientific studies on ferroptosis related to GC, as shown in Table 1, which highlights the ten most prolific countries. China stands out as the foremost contributor, boasting 346 publications and a substantial academic impact reflected in 7,167 citations. The United States and Japan rank next, with 17 and 5 publications and 52 and 64 total citations, respectively.

Figure 3(A, B) depict the global network of scientific collaboration, where the size of each node reflects the publication volume of different nations, and the thickness of the lines connecting them signifies the strength of their international partnerships. China's collaborative ties with 16 nations highlight its crucial position within this worldwide network, particularly showcasing its substantial contributions to the study of ferroptosis in GC. Notably, the academic interactions between China and the United States are the most prevalent, with a collaboration intensity index of 14. This illustrates the impressive research achievements realized by scholars from both countries in this advanced area, underscoring their exceptionally strong scientific alliance.

In Figure 3(C), two unique patterns of collaboration are depicted: Single Country Publications (SCP), where all authors belong to the same nation, and Multinational Collaborative Publications (MCP), which involve research partnerships among researchers from various countries. Analysis of the data reveals that China and the United States exhibit the most extensive international cooperation in this area. Nevertheless, it is important to highlight that a considerable share of collaborative research is still carried out among scholars within China itself.

Globally, the volume of citations has surged dramatically, highlighting the vigorous advancement and significant expansion of this research domain. In Figure 3(D), the remarkable citation achievements of the top ten nations are depicted, with the red curve clearly showcasing the increase in citations among leading countries. Between 2017 and 2025, the United States is at the forefront of publication growth, boasting an intensity score of 1.15, trailed by Canada at 0.83 and Japan at 0.78. This pattern indicates that keeping track of scientific progress in the United States can be instrumental in pinpointing new trends and key areas of focus within particular research fields.

3.3 Institutional Analysis

By conducting a thorough statistical review of pertinent literature, we discovered 439 research institutions that have published academic articles on ferroptosis in GC. From this group, we focused on 31 institutions that each had over five publications for a visual analysis using VOSviewer software. As shown in Figure 4(A), the resulting network map features 29 research nodes and 57 connecting lines. The size of each node reflects the volume of publications from the institution, while the lines illustrate the extent of collaborative research among the institutions, with thicker lines signifying stronger partnerships. Notably, Southern Medical University, Fudan University, and Shanghai Jiao Tong University have formed particularly strong networks of academic collaboration.

3.4 Analysis of Published Journals and Highly Cited Journals

Our analysis of journal publications indicates that 189 academic journals have contributed research on GC ferroptosis. The top 10 journals by publication count are detailed in Table 2, while Table 3 highlights the 10 journals with the highest citation rates. The findings show that FRONTIERS IN PHARMACOLOGY leads with 13 publications (IF=4.8), followed by SCIENTIFIC REPORTS with 11 (IF=3.9), FRONTIERS IN CELL AND DEVELOPMENTAL BIOLOGY with 8 (IF=4.3), REDOX BIOLOGY with 8 (IF=11.9), and CELL DEATH & DISEASE with 7 (IF=9.6). These journals are pivotal in advancing research on ferroptosis in GC and deserve focused attention from scholars. Additionally, Table 3 illustrates that *Cell* and *Nature* lead all cited journals with 591 and 488 citation-related frequencies, respectively, underscoring their prominent influence in this research domain.

In this research, a threshold of three publications was set as the minimum requirement for journal inclusion, leading to the selection of 34 influential

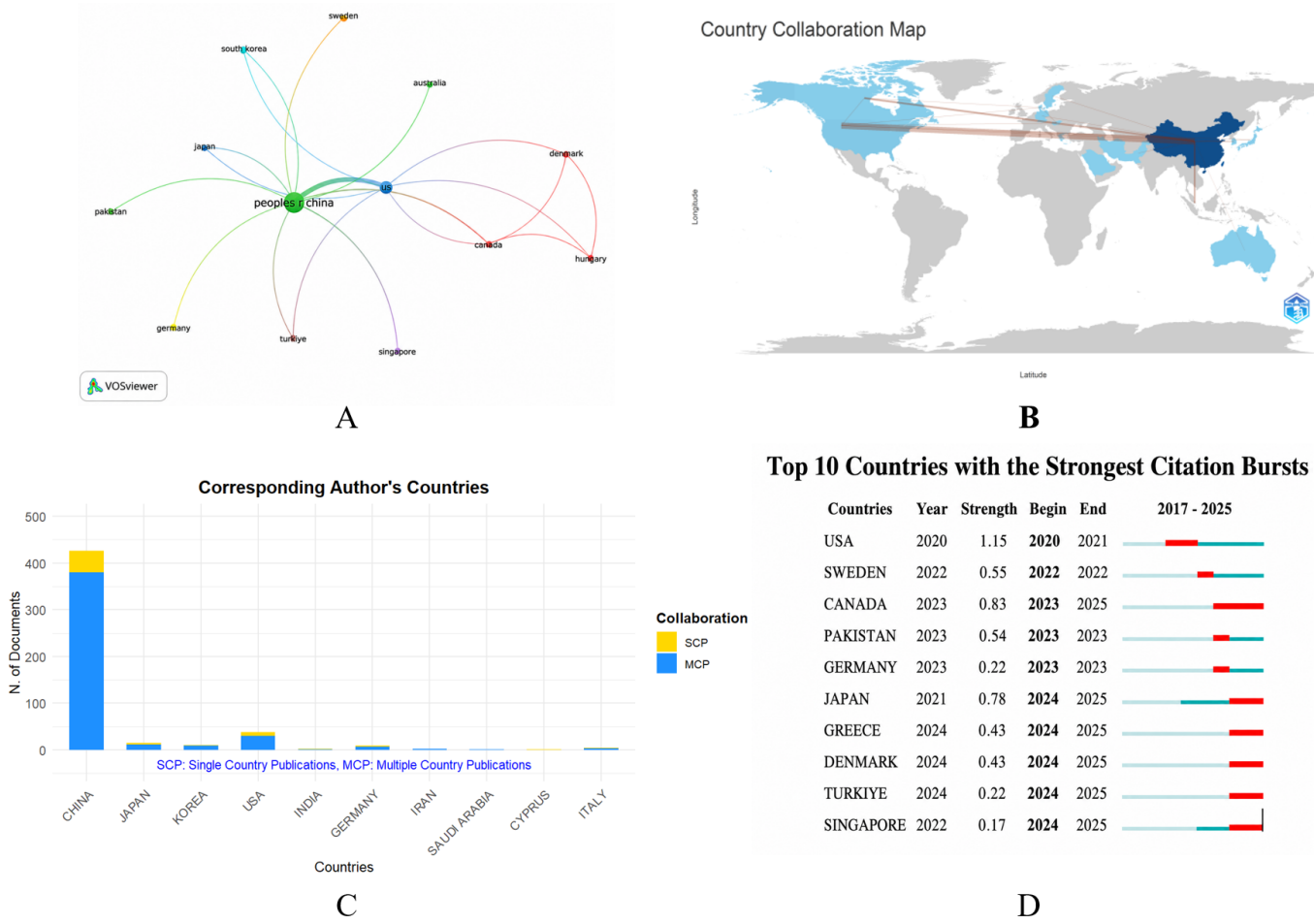

Figure 3. Contributions of different countries to ferroptosis research in GC. (A. Map illustrating national collaborative contributions; B. Global map showcasing international partnerships; C. Leading 10 nations with the highest number of corresponding authors; D. Top 10 countries/regions exhibiting the greatest citation surge rates).

Table 2. Top 10 Journals with the Highest Number of Publications.

Ranking	Journal Name	Number of Documents	Impact Factor (IF)	H-index	JCR Category	Country of Origin
1	FRONTIERS IN PHARMACOLOGY	13	4.8	62	1	Switzerland
2	SCIENTIFIC REPORTS	11	3.9	149	1	United Kingdom
3	FRONTIERS IN CELL AND DEVELOPMENTAL BIOLOGY	8	4.3	93	1	Switzerland
4	REDOX BIOLOGY	8	11.9	57	1	Netherlands
5	CELL DEATH DISEASE	7	9.6	85	1	United Kingdom
6	FRONTIERS IN GENETICS	7	2.8	61	2	UNITED STATES
7	INTERNATIONAL IMMUNOPHARMACOLOGY	7	4.7	98	2	Netherlands
8	FRONTIERS IN ONCOLOGY	6	3.3	60	2	Switzerland
9	GASTRIC CANCER	6	5.1	68	1	Japan
10	AGING-US	5	3.9	73	2	United States

journals for analysis using VOSviewer. This process resulted in the development of a collaborative network map of journals (see Figure 5(A)). The findings highlighted notable partnerships among these journals, with FRONTIERS IN CELL AND DEVELOPMENTAL BIOLOGY standing out for its

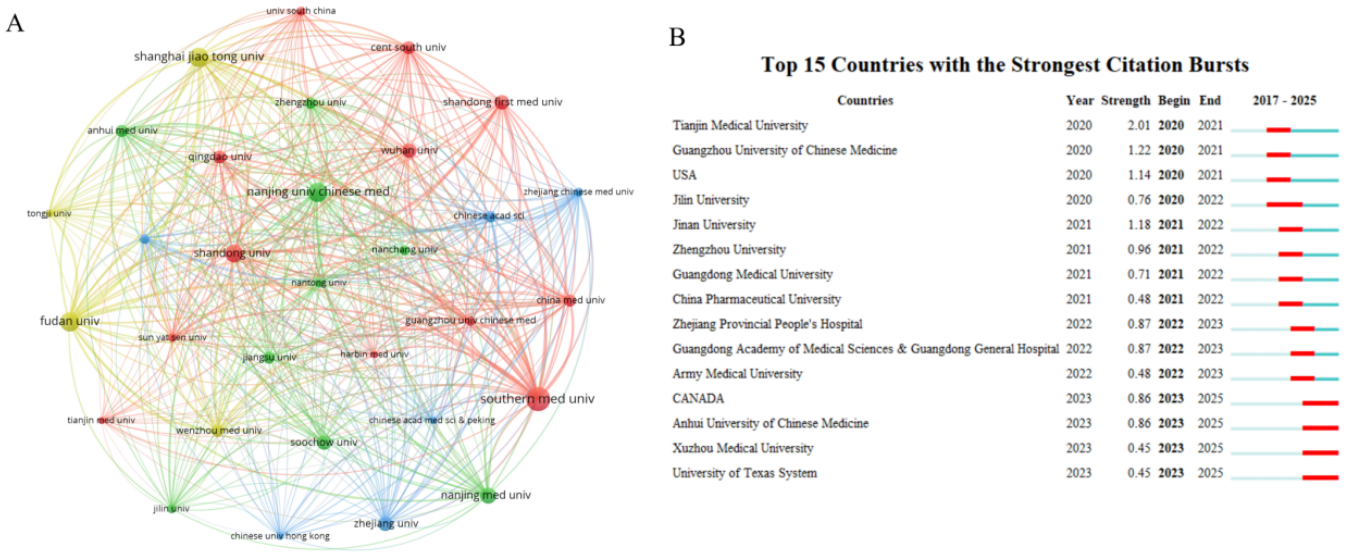

Figure 4. Visualization of institutions conducting research on GC ferroptosis. (A. Institutional Collaboration Donation Map. B. Top 15 Institutions with the Highest Number of Publications.)

Table 3. Top 10 Most Cited Journals.

Ranking	Journal Name	Citations-Related Frequency	Impact Factor (IF)	H-index	JCR Category	Country of Origin
1	CELL	591	42.3	705	1	United States
2	NATURE	488	48.5	1096	1	United Kingdom
3	CELL DEATH DIS	388	9.6	85	1	United Kingdom
4	NAT COMMUN	337	15.7	248	1	United Kingdom
5	MOL CANCER	313	33.9	103	1	United Kingdom
6	REDOX BIOL	310	11.9	57	1	NETHERLANDS
7	CA-CANCER J CLIN	268	232.4	144	1	United States
8	CELL DEATH DIFFER	256	15.7	193	1	United Kingdom
9	INT J MOL SCI	241	4.9	114	1	United States
10	FRONT ONCOL	234	3.3	60	2	Switzerland

collaborations with 22 leading research institutions. The study established a baseline of three papers per journal and identified 34 key journals for visualization analysis, which facilitated the creation of a journal collaboration network diagram (Figure 5(A)). This diagram illustrated strong collaborative ties among the journals, particularly with one journal forming connections with 22 prominent research entities. Additionally, a dual-map overlay analysis uncovered two primary citation pathways, showcasing trends in knowledge transfer among various journals (refer to Figure 5(C)). The left side of the map indicates the disciplines of the published works, while the right side reflects the source fields of the cited literature. Specifically, articles from journals in molecular biology, immunology, medicine, and clinical research frequently reference works from related areas like molecular biology and genetics on the right. Moreover, citation links were also observed between journals in disciplines such as physics, materials science, and chemistry, visually representing the flow of knowledge and research interactions across diverse fields.

3.5 Author and Co-cited Author Analysis

In the domain of research examining the link between ferroptosis and GC, a total of 2,458 researchers globally have made noteworthy contributions. As shown

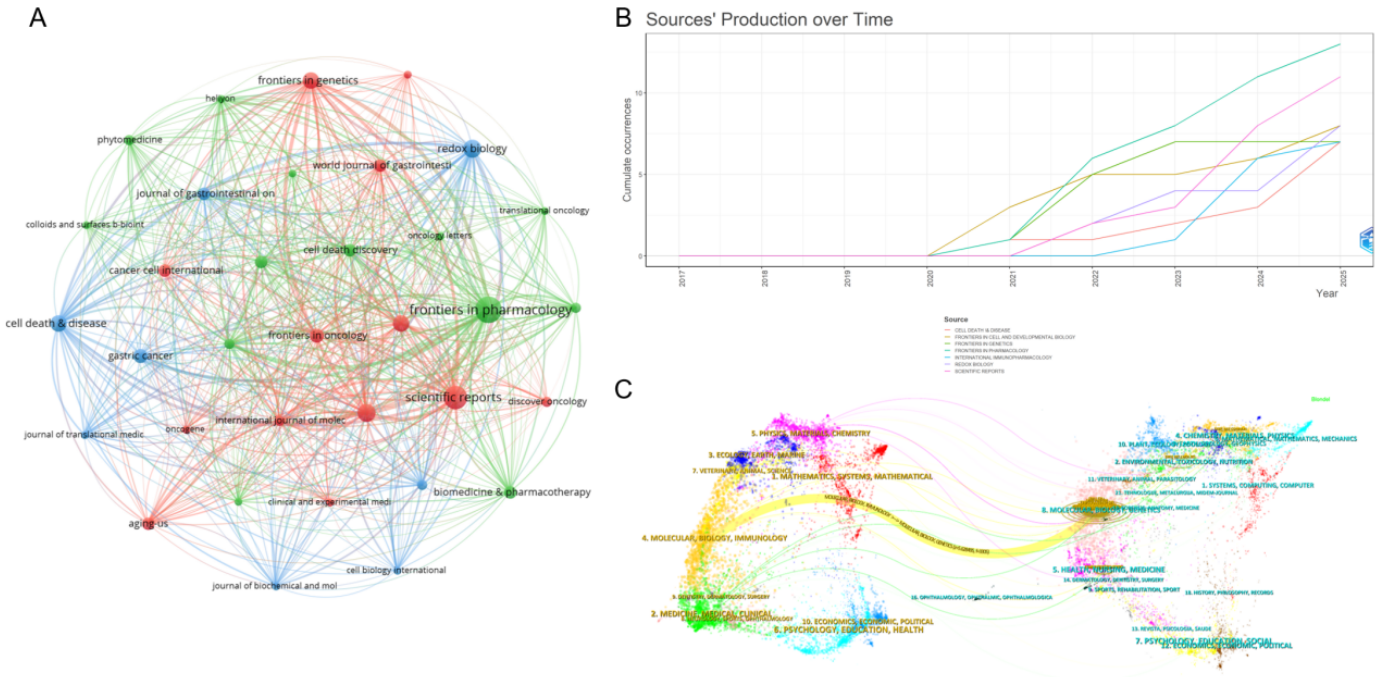

Figure 5. Analysis of published journals and highly cited journals on GC ferroptosis. (A. Journal collaboration map. B. Journal annual publication trend. C. Journal dual-map overlay.)

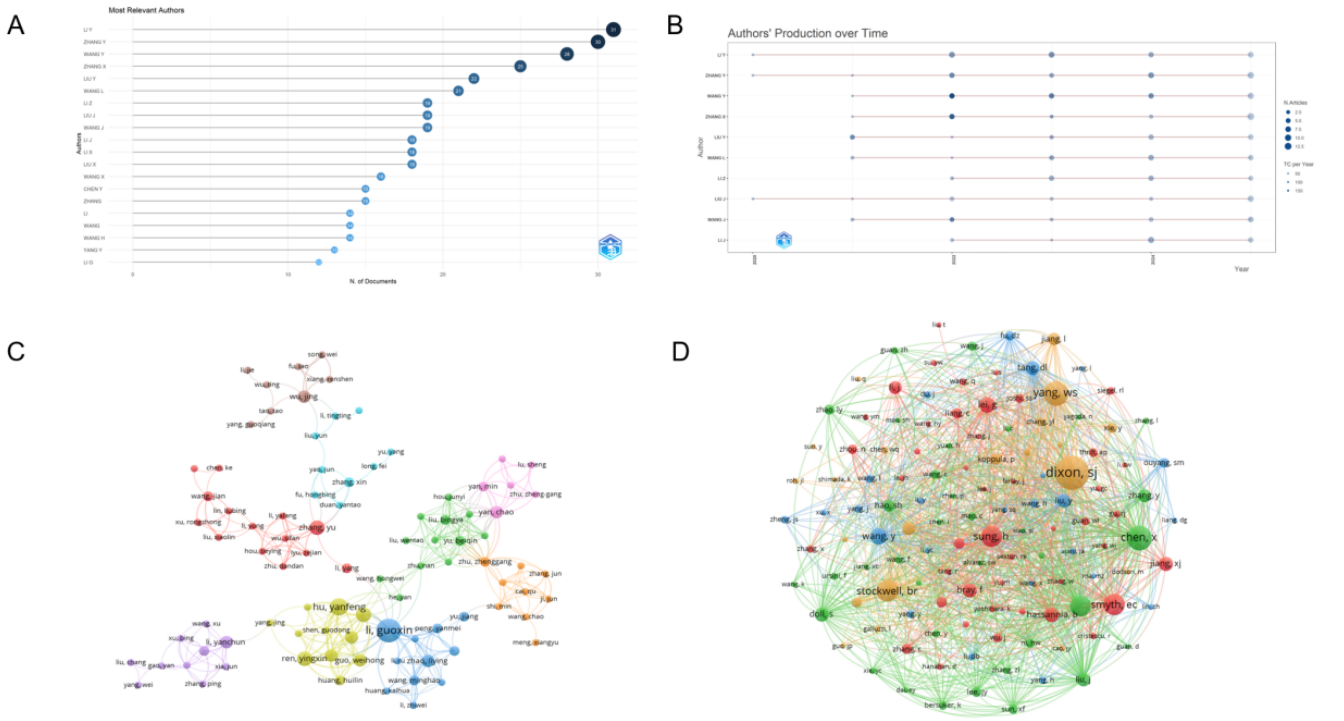

Figure 6. Analysis of authors and co-cited authors in GC ferroptosis research. (A. list of the 20 most prolific writers. B. Yearly trends in the publication rates of the 10 authors with the highest output. C. A graphical representation of the network of author collaborations. D. Partnerships among frequently cited authors.)

in Figure 6(A), Li Y from China leads with 31 publications, followed by Zhang Y with 30 and Wang Y with 28, with their yearly publication patterns illustrated in Figure 6(B). Importantly, Professor Tang Daolin, a trailblazer in this area, was the first to explore the connection between GC and

ferroptosis, and his scholarly impact continues to be felt. The collaboration network among authors was created using VOSviewer software (Figure 6(C)), where different colors represent various research groups. The findings indicate that members of the same group exhibit strong collaborative ties, while inter-group cooperation is somewhat limited. Co-citation analysis in Figure 6(D) highlights three leading scholars—Dixon S.J. (n=227), Chen X (n=145), and Yang W.S. (n=142)—who have the highest citation counts, reflecting their significant academic impact and contributions in this area.

3.6 Co-citation Analysis

Among 362 research papers focusing on ferroptosis and GC, researchers identified 13,456 co-cited references. Through screening, we ultimately determined 31 key publications that were co-cited over 20 times, based on which we constructed a co-citation network map (Figure 7(A)). This map illustrates the network of references that were simultaneously cited by at least one paper. Table 4 lists the top 10 most frequently co-cited publications, with 9 originating from Chinese researchers and only 1 from Japan. Notably, Chinese scholar WANG Y has made significant contributions in this research field, demonstrating considerable influence. In GC research, the team led by WANG Y investigated the mechanism by which the Wnt/β-catenin signaling pathway confers resistance to ferroptosis through the regulation of Glutathione Peroxidase 4(*GPX4*). This publication has received widespread citations. The concept of ferroptosis was first introduced in a 2012 publication in Cell. Subsequently, in 2014, Wan Seok Yang's research group revealed in Cell the crucial role of *GPX4* in regulating ferroptosis. These two studies provided essential theoretical foundations for the development of ferroptosis as a scientific field.

The phenomenon known as citation surge occurs when a specific academic paper garners an unusually high volume of citations in a brief timeframe. This trend can help pinpoint innovative research avenues within the discipline. The chart provided illustrates citation statistics for the top 20 articles based on citation frequency, with blue lines denoting the duration of citations and red segments highlighting peak citation intervals. Remarkably, the 2017 article authored by Stockwell BR's team in the journal *Cell* holds the top position, boasting a citation intensity score of 13.01. Other works also show notable citation activity; for example, Bray F's 2018 study, published in *CA-Cancer J Clin*, earned a citation intensity score of 8.63. Both papers stand out significantly compared to their peers. Particularly noteworthy is Dodson M's 2019 publication in REDOX BIOL, which is anticipated to maintain its citation growth through 2025. This trend emphasizes the lasting academic significance of these findings in both the present and future, showcasing the ongoing potential for development and the innovative scholarly importance of this research area.

Data from research suggests that performing clustering analyses on shared literature resources is an effective way to pinpoint research hotspots within various academic disciplines. Visualization assessments show that the modularity index for the initial map is 0.4684, while the subsequent map shows an improvement to 0.5571, both surpassing the threshold of 0.3, which validates the presence of significant clustering effects. Furthermore, the average silhouette coefficient for the first map stands at 0.5574, rising to 0.6593 in the second map. Although there are slight variations, a thorough assessment confirms the reliability of the cluster analysis. By employing keyword clustering techniques, we meticulously examined pertinent literature and uncovered several key thematic clusters, such as research in metabolomics, characteristics of the tumor microenvironment, therapies in traditional Chinese medicine, mechanisms of tumor invasion, comprehensive treatment approaches, evaluations of drug sensitivity, Mendelian randomization studies, and the Phosphatidylinositol 3-kinase (*PI3K*) signaling pathway. When combined with timeline visualization data, the changing trends across various research domains are clearly illustrated. As depicted in the figure, studies on transcription initiation factors like Activating Transcription Factor 4(ATF4) (Cluster #6) commenced relatively early but have recently shown a downward trend, suggesting that this area has reached a more stable phase. In contrast, the densely clustered red nodes in immunotherapy research (Cluster #0) highlight its significant status as a leading edge in the field, effectively showcasing the dynamic shifts in research focus within this domain.

3.7 Keyword Analysis

3.7.1 Keyword Co-occurrence Analysis

The essential concepts of a research paper are succinctly represented by its keywords. By constructing a keyword co-occurrence network, we can clarify the primary focus and emerging trends in a particular academic discipline. In this analysis, we employed VOSviewer software to examine 1,254

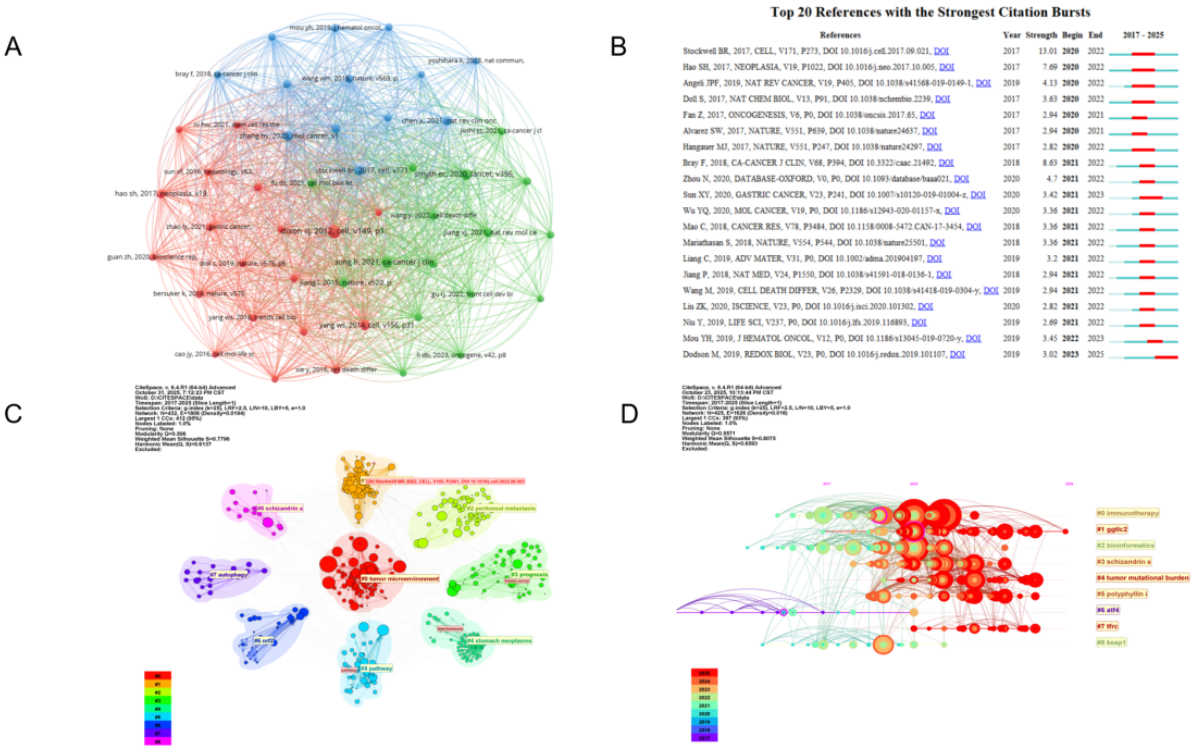

Figure 7. Co-citation reference analysis of GC ferroptosis research. (A. Network diagram illustrating documents with co-citation frequencies above 20. B. The 15 most frequently cited references exhibiting the highest burst citation rates. C. Cluster diagram representing co-cited references. D. Chronological representation of co-cited references.)

keywords, filtering out terms with a frequency of fewer than five occurrences to generate the keyword co-occurrence network (see Figure 8(A)). During this process, we eliminated keywords that were deemed too generic to provide specific contextual insight, such as 'death' and 'cell.' The top ten keywords identified were ferroptosis, gastric cancer, apoptosis, cell death, expression, metabolism, activation, resistance, pathway, and *GPX4*. The timeline visualization in Figure 8(C) illustrates the evolutionary trajectory and interrelationships of these keywords.

3.7.2 Keyword Citation Burst Analysis

By examining the distribution patterns of frequently cited terms, researchers can predict emerging research areas and future developments within the field. Using CiteSpace software, we identified 20 essential keywords that exhibited a significant surge in citation frequency over the last ten years, as depicted in Figure 8(B). Of all the metrics analyzed, tumor microenvironment demonstrated the highest burst strength, with a burst strength index of 3.61, followed by form and identification. Additionally, immune infiltration has proven to be the most enduring research focus, first noted in 2021 and experiencing significant growth from 2021 to 2023. Current research fronts predominantly focus on keywords such as ferroptosis, gastric cancer, resistance, identification, immunotherapy, and tumor microenvironment. Among these, identification, resistance, gastric cancer, immunotherapy, and tumor microenvironment have emerged as pivotal research avenues.

4 Discussion

This study employed bibliometric methods and visual analysis tools based on the Web of Science database (up to October 20, 2025). With the assistance of VOSviewer, CiteSpace and other analytical tools, a total of 362 English publications on ferroptosis in gastric cancer, published in 189 journals by 2,458 researchers from 16 countries, were systematically analyzed. Publication trends, academic collaboration networks and keyword co-occurrence maps were constructed in this study, which clarified the research hotspots focusing on the molecular regulatory mechanisms of ferroptosis.

In addition, this systematic review intensively discussed the potential mechanism of ferroptosis in the initiation and progression of gastric cancer, which was elaborated from three perspectives. Firstly, the regulatory pathways related to lipid metabolism underlying ferroptosis in gastric cancer; secondly, the regulatory effects of transcription factors and signaling pathways on ferroptosis in gastric cancer;

Table 4. Top 10 most co-cited references.

Rank	Title	Published Year	First Author	Journal	Co-citations	Publication Type	Countries
1	Wnt/beta-catenin signaling confers ferroptosis resistance by targeting *GPX4* in gastric cancer	2022	WANG Y	CELL DEATH DIFFER	37	Research	China
2	Identification of ferroptosis as a novel mechanism for antitumor activity of natural product derivative a2 in gastric cancer	2021	LIU Y	ACTA PHARM SIN B	19	Research	China
3	Levobupivacaine Induces Ferroptosis by miR-489-3p/*SLC7A11* Signaling in Gastric Cancer	2021	MAO SH	FRONT PHARMACOL	17	Research	China
4	Hypoxia inducible lncRNA-CBSLR modulates ferroptosis through m6A-YTHDF2-dependent modulation of CBS in gastric cancer	2022	YANG H	J ADV RES	14	Research	China
5	Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries	2023	XU X	REDOX BIOL	14	Research	China
6	CPEB1 enhances erastin-induced ferroptosis in gastric cancer cells by suppressing twist1 expression	2021	WANG J	IUBMB LIFE	12	Research	China
7	Polyphyllin B Suppresses Gastric Tumor Growth by Modulating Iron Metabolism and Inducing Ferroptosis	2023	HU C	INT J BIOL SCI	10	Research	China
8	Role of ferroptosis and ferroptosis-related non-coding RNAs in the occurrence and development of gastric cancer	2022	LU L	FRONT PHARMACOL	8	Research	China
9	Identification and validation of a novel ferroptosis-related gene model for predicting the prognosis of gastric cancer patients	2021	LIU G	PLOS ONE	7	Review	China
10	*GPX4* Regulates Tumor Cell Proliferation via Suppressing Ferroptosis and Exhibits Prognostic Significance in Gastric Cancer	2022	SUGEZAWA K	ANTICANCER RES	6	Research	Japan

thirdly, the tumor microenvironment mechanisms linking ferroptosis to chemotherapy resistance in gastric cancer. This paper also systematically reviewed iron ions as one of the potential therapeutic targets for gastric cancer, and summarized pharmacological molecules involved in the regulation of gastric cancer ferroptosis. The relevant discussions are elaborated in the following sections.

4.1 Research Summary

Gastric cancer remains one of the most formidable malignancies worldwide, ranking as the fifth most common cancer and the fourth leading cause of cancer-related mortality. Its incidence is particularly elevated in East Asia, Central and South America, and Eastern Europe, with a higher prevalence in males. Despite advances in surgical, chemotherapeutic, and targeted interventions, the five-year survival rate remains approximately 20%, largely due to late-stage diagnosis, chemoresistance, and tumor recurrence. These clinical challenges underscore the urgent need for innovative therapeutic strategies. Ferroptosis, a recently characterized form of regulated cell death driven by iron-dependent lipid peroxidation, has emerged as a promising avenue for cancer treatment. Notably, ferroptosis has been shown to suppress tumor growth and reverse drug resistance, particularly in mesenchymal and metastatic cancer cells [19, 20, 22].

In the present study, we employed bibliometric and visualization analyses to systematically evaluate 362 publications on ferroptosis in gastric cancer indexed in the Web of Science database up to October 20, 2025. Using tools such as VOSviewer and CiteSpace, we quantitatively assessed research trends, core contributors, and evolving hotspots. Our key findings reveal a dramatic surge in research output since 2021, with China, the United States, and Japan leading contributions. Mechanistically, central regulators such as *GPX4* and Solute Carrier Family 7 Member 11(*SLC7A11*) remain focal points, while emerging themes including the tumor microenvironment, drug resistance, and immunotherapy reflect a paradigm shift toward translational applications. These results provide a data-driven roadmap for

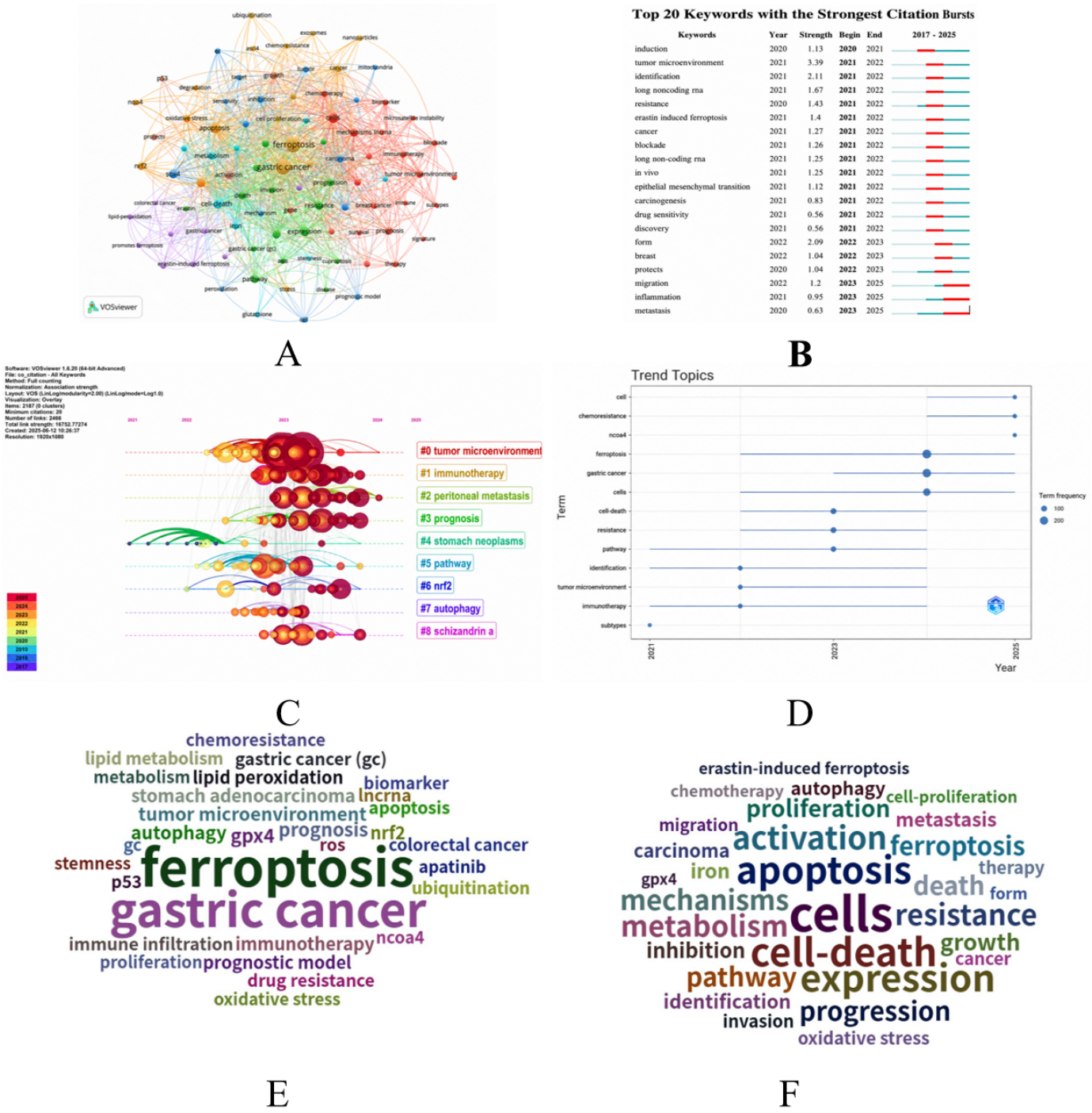

Figure 8. Key terms in GC ferroptosis research. (A. Graph depicting keyword networks. B. The 20 most prominent keywords exhibiting the highest citation surges. C. Chronological representation of author keywords. D. Evolution of keyword trends over time. E. Map illustrating author keywords. F. Visual representation of keywords.)

future investigations, highlighting critical areas for mechanistic exploration, biomarker discovery, and therapeutic innovation in ferroptosis-based gastric cancer treatment.

Building upon the systematic mapping of the research landscape, the identified core keywords and emergent clusters provide a strategic framework for subsequent multi-omics investigations. The centrality of terms like '*GPX4*' and 'tumor microenvironment' underscores their established roles as critical nodes in the ferroptosis regulatory network, guiding hypothesis-driven biomarker discovery. For instance, the keyword '*GPX4*' aligns with foundational studies confirming its role as a master regulator of ferroptosis by detoxifying lipid peroxides [2]. Similarly, the prominence of 'tumor microenvironment' reflects

a growing understanding that non-malignant stromal cells, such as cancer-associated fibroblasts (CAFs), can profoundly influence tumor cell ferroptosis susceptibility through paracrine signaling, as demonstrated by the secretion of exosomal microRNA-522(*miR-522*) that suppresses Arachidonate 15-Lipoxygenase(*ALOX15*) [36]. Furthermore, ferroptosis-related long non-coding RNA signatures have shown promise in predicting prognosis in gastric cancer, further highlighting the translational relevance of ferroptosis within the tumor microenvironment [20]. The evolution of keywords from fundamental 'cell death' and 'metabolism' towards 'resistance' and 'immunotherapy' signifies a paradigm shift from mechanistic discovery to therapeutic application. This trend suggests that future therapeutic strategies should not only target intrinsic ferroptosis pathways in cancer cells but also consider the extrinsic modulation of the tumor immune microenvironment, where inducing ferroptosis can release immunogenic signals and synergize with checkpoint inhibitors [21]. Furthermore, the identification of 'Mendelian randomization' as a cluster highlights an emerging methodological frontier; integrating this genetic epidemiology approach with ferroptosis gene signatures could help distinguish causal drivers of gastric cancer risk from mere correlative associations, thereby prioritizing the most promising targets for functional validation.

The high co-citation analysis pinpointing *GPX4* as a central hub is corroborated by extensive mechanistic studies, yet its regulatory complexity in gastric cancer warrants deeper exploration. Beyond its canonical antioxidant function, post-translational modifications of *GPX4*, such as its regulation by acetylation or phosphorylation, remain largely uncharted in the gastric cancer context and represent a significant gap in our understanding of its context-dependent activity. While the Wnt/β-catenin-*GPX4* axis is a validated pathway conferring ferroptosis resistance [as indicated by high-impact studies], other crucial signaling cascades are implicated. For example, the Kelch-like ECH-associated protein 1 (Keap1)/Nuclear factor erythroid 2-related factor 2(Nrf2)/*SLC7A11* axis, which upregulates *SLC7A11* and *GPX4*, is a well-established resistance mechanism, and its inhibition by Activating Transcription Factor 3 (ATF3) has been shown to re-sensitize cells to cisplatin by promoting ferroptosis [22]. Conversely, the Sirtuin 6 (SIRT6) SIRT6/Keap1/Nrf2/*GPX4* pathway has been identified as a mediator of sorafenib resistance [23]. This suggests a complex, interconnected network where multiple upstream signals converge on key ferroptosis executors like *GPX4* and *SLC7A11*. Translating these protein-centric findings into clinical applications requires correlating their expression or activity with patient outcomes. Emerging bioinformatics models have begun this work, constructing prognostic signatures based on ferroptosis-related genes across multiple gastrointestinal cancers, which show promise in stratifying patient risk and predicting immunotherapy response [24]. However, these computational predictions necessitate rigorous validation through immunohistochemistry on clinical cohorts to establish *GPX4* or *SLC7A11* as reliable biomarkers or actionable therapeutic targets. The prominence of 'metabolism' in keyword analysis is mechanistically grounded, as ferroptosis is intrinsically linked to profound metabolic reprogramming in cancer cells. Gastric cancer cells exhibit specific metabolic vulnerabilities that dictate their sensitivity to ferroptotic death. A key determinant is the polyunsaturated fatty acid (PUFA) biosynthesis pathway, where the expression of enzymes like Elongation of very long chain fatty acid protein 5 (*ELOVL5*) and Fatty acid desaturase 1 (*FADS1*) differs between mesenchymal and intestinal-type gastric cancers, directly influencing the cellular pool of peroxidizable lipids and thereby ferroptosis sensitivity [25]. This metabolic heterogeneity suggests that profiling lipid composition could predict therapeutic response. Furthermore, amino acid metabolism, particularly cysteine uptake via the xCT transporter (*SLC7A11*), is a critical checkpoint; its downregulation by *p53*, as seen with Tanshinone IIA treatment, depletes glutathione and triggers ferroptosis [19]. To systematically identify such vulnerabilities, metabolomics profiling of patient-derived samples—such as organoids or paired tumor/normal tissues—is essential. This approach can delineate subtype-specific metabolic signatures and uncover metabolites that serve as biomarkers for ferroptosis sensitivity. Extending beyond cell-autonomous mechanisms, systemic metabolic factors like obesity can alter the tumor microenvironment, potentially affecting nutrient availability and inflammatory signals that modulate ferroptosis. For instance, cholesterol synthesis has been linked to an immunosuppressive microenvironment, and its inhibition by simvastatin can induce ferroptosis and enhance anti-programmed death-1 (anti-PD-1) efficacy in microsatellite stable

GC [26], illustrating a direct link between host metabolism, tumor cell death, and immune response.

4.2 The mechanism of ferroptosis in GC

We systematically reviewed and adopted bibliometric analysis to explore the global research trends of ferroptosis in GC. Therefore, this study mainly summarizes the potential mechanisms of ferroptosis in the occurrence and progression of GC. The mechanistic summary is elaborated from three aspects: regulatory pathways related to lipid metabolism, regulation by transcription factors and signaling pathways, as well as tumor microenvironment mechanisms involved in chemotherapy resistance.

4.2.1 Lipid Metabolism-related Regulatory Pathways

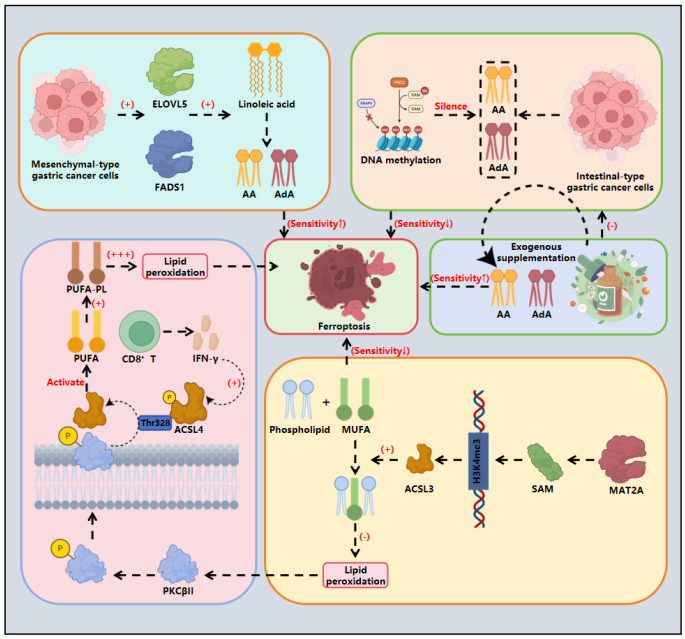

Figure 9. Regulatory pathways of ferroptosis related to lipid metabolism.

The *ELOVL5*- and *FADS1*-mediated pathway is characterized by elevated levels of these enzymes in mesenchymal-type GC cells, which facilitates the conversion of linoleic acid into arachidonic acid (AA) and adrenic acid (AdA), thus increasing susceptibility to ferroptosis [25]. As shown in Figure 9, in contrast, intestinal-type GC sees the silencing of these proteins due to DNA methylation, leading to ferroptosis resistance. Nevertheless, introducing AA from external sources has been found to restore sensitivity to ferroptosis [25]. The Methionine Adenosyltransferase 2A (*MAT2A*)-Acyl CoA Synthetase Long Chain Family Member 3 (ACSL3) pathway demonstrates that S-adenosylmethionine (SAM), produced by *MAT2A*, activates ACSL3 via increased histone H3 trimethylation at lysine 4 (*H3K4me3*) in the promoter region. This activation encourages the integration of monounsaturated fatty acids (MUFA) into phospholipids, reduces lipid peroxidation, and boosts resistance to ferroptosis in GC cells [27]. The positive feedback loop involving Protein Kinase C beta-II isoform(PKCβII) and Acyl-CoA Synthetase Long-Chain Family Member 4(*ACSL4*) shows that a moderate buildup of lipid peroxides can trigger the phosphorylation of protein kinase CβII (PKCβII), aiding its movement to the cell membrane. Once activated, PKCβII enhances the ability of *ACSL4* to activate polyunsaturated fatty acids (PUFAs). This enhancement occurs through the phosphorylation of the Threonine 328 (*Thr328*) site on *ACSL4*. Consequently, this process promotes the production of PUFA-phospholipids (PUFA-PL). This mechanism intensifies lipid peroxidation to critical levels, ultimately leading to ferroptosis [28]. Additionally, Interferon-gamma (IFN-γ) released by Cluster of Differentiation 8-positive T lymphocytes ($CD8^+$T cells) can increase *ACSL4* expression. This upregulation boosts the activity of the PKCβII-*ACSL4* pathway, thereby promoting ferroptosis in GC cells. These findings support the rationale for combining immune checkpoint inhibitors (ICI) with PUFA supplements [28].

4.2.2 Transcription Factors and Signaling Pathway Regulation

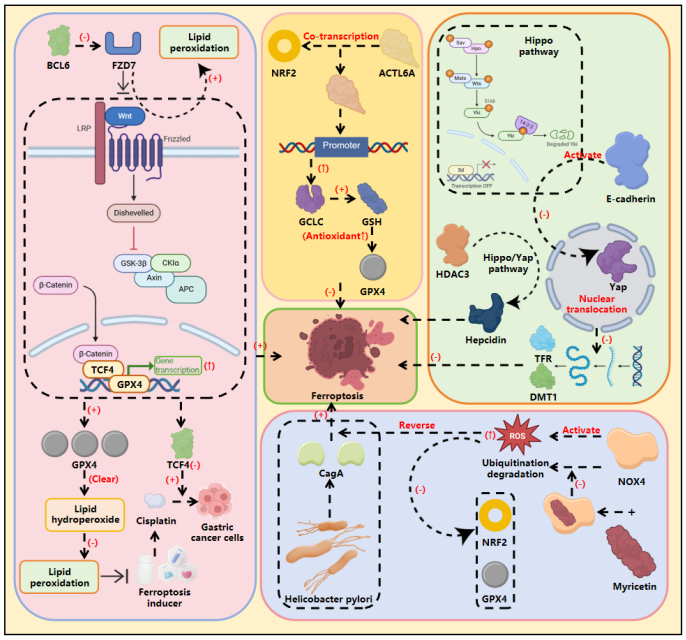

Figure 10. Transcription factor-mediated ferroptosis.

As shown in Figure 10, the Wingless-type MMTV integration site family(Wnt)/β-catenin signaling

pathway plays a crucial role in conferring resistance to ferroptosis. Upon activation of the Wnt pathway, β-catenin translocates to the nucleus. In the nucleus, β-catenin interacts with Transcription Factor 4 (*TCF4*) to form a transcriptional complex. This complex binds to the *GPX4* promoter, leading to increased *GPX4* expression [30]. In parallel, Stearoyl-CoA Desaturase 1 (*SCD1*) has been shown to promote ferroptosis resistance in gastric cancer stem cells through the SQLE/cholesterol/mTOR signalling pathway [29]. This upregulation enhances *GPX4* ability to eliminate lipid hydroperoxides and inhibit lipid peroxidation, thereby providing resistance to ferroptosis inducers like cisplatin in GC cells. A lack of *TCF4* significantly heightens the susceptibility of these cells to ferroptosis induced by cisplatin, both in laboratory settings and in living organisms. Furthermore, B-cell lymphoma 6 protein(*BCL6*) contributes to lipid peroxidation and ferroptosis by inhibiting the Wnt receptor Frizzled Class Receptor 7(*FZD7*), which disrupts the β-catenin/Tumor Protein P63(*TP63*)/*GPX4* signaling pathway [31]. In the Nuclear Factor Erythroid 2-Related Factor 2 (*NRF2*) pathway, there exists an axis comprising actin-like protein 6A (*ACTL6A*), *NRF2*, and the Glutamate-Cysteine Ligase Catalytic Subunit (*GCLC*). This axis functions via *ACTL6A*. Specifically, *ACTL6A* serves as a co-transcriptional factor for *NRF2*.The complex binds to the *GCLC* promoter. This binding leads to increased *GCLC* expression. Furthermore, it enhances the synthesis of glutathione (GSH). The rise in GSH levels boosts the antioxidant function of *GPX4*, thereby preventing ferroptosis in GC cells [32]. In the NADPH Oxidase 4(*NOX4*)-*NRF2*-*GPX4* pathway, myricetin binds to *NOX4*, preventing its degradation and enhancing its stability. This results in increased Reactive Oxygen Species(ROS)production while simultaneously inhibiting *NRF2* transcriptional activity, which decreases *GPX4* expression. This dual action significantly promotes ferroptosis in GC cells and can counteract the resistance to ferroptosis caused by *Helicobacter pylori* Cytotoxin-associated gene A(CagA) [33]. The Hippo pathway regulates intercellular homotypic interactions through E-cadherin, activating the Hippo signaling cascade and preventing the nuclear translocation of Yes-associated protein (*Yap*). The Hippo pathway regulates intercellular homotypic interactions through E-cadherin, activating the Hippo signaling cascade and preventing the nuclear translocation of Yes-associated protein (*YAP*). Inhibition of *YAP* activity reduces the expression of iron metabolism-related genes, such as transferrin receptor (*TFR*) and divalent metal transporter 1 (*DMT1*), thus maintaining iron homeostasis and inhibiting ferroptosis [34]. Additionally, Histone Deacetylase 3(*HDAC3*) has been shown to modulate hepcidin expression via the Hippo/*Yap* pathway, regulating systemic iron homeostasis and ferroptosis [35], a mechanism with potential implications for iron-dependent cell death in gastric cancer.

4.2.3 *Mechanisms of Tumor Microenvironment in Chemotherapy Resistance*

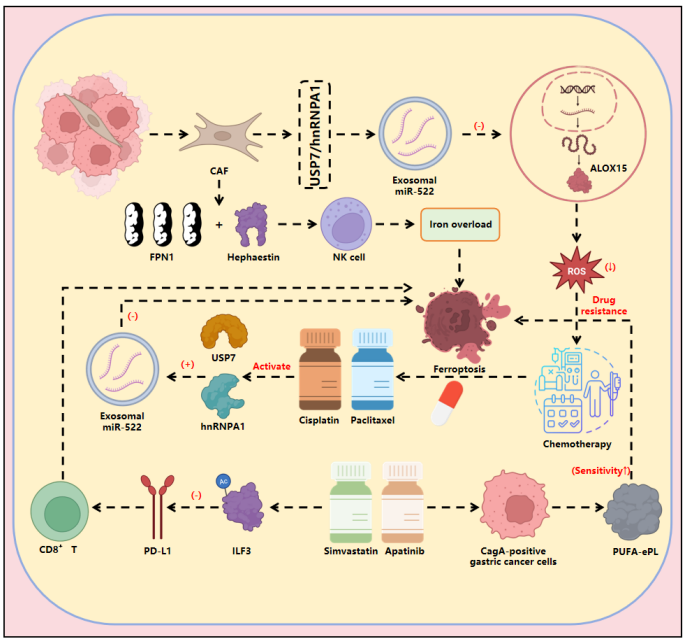

Figure 11. Tumor microenvironment and chemotherapy-induced ferroptosis.

As shown in Figure 11, cancer-associated fibroblasts (CAFs) influence tumor behavior by releasing exosomal microRNA-522(*miR-522*) via the Ubiquitin-Specific Peptidase 7(*USP7*)/Heterogeneous Nuclear Ribonucleoprotein A1(*hnRNPA1*) pathway, which downregulates Arachidonate 15-Lipoxygenase(*ALOX15*)expression. This action leads to a decrease in lipid ROS accumulation, playing a role in the development of chemoresistance in GC [36]. Additionally, Cancer-Associated Fibroblasts(CAFs) enhance the iron overload in natural killer (NK) cells by increasing the levels of iron export proteins such as Ferroportin 1(*FPN1*) and Hephaestin, which triggers ferroptosis and diminishes their ability to combat tumors [37]. The relationship between chemotherapy agents and ferroptosis indicates that cisplatin and paclitaxel stimulate the release of *miR-522* through the activation of the *USP7*/*hnRNPA1* pathway, which in turn hinders ferroptosis in GC cells. Additionally, simvastatin

decreases Programmed death-ligand 1(PD-L1) levels and boosts $CD8^+$ T cell-induced ferroptosis in these cells by lowering the acetylation of Interleukin Enhancer-Binding Factor 3(*ILF3*) at Histone H3 Lysine 14(*H3K14*) [38]. Furthermore, apatinib shows increased effectiveness against CagA-positive GC cells by facilitating the synthesis of Polyunsaturated Ether Phospholipids(PUFA-ePL) and increasing their susceptibility to ferroptosis [39].

4.3 Targeted Therapeutic Molecules for Ferroptosis in GC

Ferroptosis is a type of regulated cell death that relies on iron and is characterized by lipid peroxidation. It has gained attention as a potential therapeutic target for the γ-glutamylcysteine ligase catalytic subunit (*GCLC*) due to its distinct mechanisms and ability to counteract resistance to standard treatments [78]. Recent studies have identified a growing number of molecular targets and therapeutic agents that modulate ferroptosis in gastric cancer, as summarized in Table 5.

Recent research has pinpointed several molecular targets that play a role in ferroptosis regulation, offering innovative approaches for treating GC. Among these targets are the glutathione (GSH)/*GPX4* pathway, where blocking *GPX4* results in the buildup of harmful lipid peroxides, and the system *SLC7A11* transporter, which is essential for cysteine uptake necessary for GSH production [15]. Disruptions in these pathways, such as the upregulation of the γ-*GCLC* by Actin-Like Protein 6A (*ACTL6A*) to sustain GSH levels, lead to ferroptosis resistance in GC cells [32]. Additionally, the circular RNA 0008035 (*circ0008035*)/*microRNA-302a* (*miR-302a*)/*E2F Transcription Factor 7* (*E2F7*) pathway has been identified. This pathway is linked to dexmedetomidine-induced ferroptosis. In this mechanism, *circ0008035* modulates *E2F7* expression by sequestering *miR-302a*. Consequently, this interaction influences iron and ROS metabolism [53]. The *NOX4*/*NRF2*/*GPX4* pathway is another significant target, highlighted by myricetin's role in stabilizing NOX4 and inhibiting the NRF2-GPX4 antioxidant pathway, which makes GC cells more susceptible to ferroptosis [33]. Furthermore, CagA from *Helicobacter pylori* enhances sensitivity to ferroptosis. This effect is mediated by an increase in PUFA-ePLs. Specifically, this process occurs via the MEK/ERK/SRF-AGPS/AGPAT3 signaling cascade. These findings suggest that CagA status could serve as a valuable biomarker for ferroptosis-inducing therapies, including Apatinib [39]. Lastly, the loss of E-cadherin in diffuse-type gastric cancer (DGC) disrupts Hippo pathway signaling, making cells more vulnerable to ferroptosis, which could be strategically targeted to address circulating metastatic cells [34]. The aforementioned targets and their corresponding therapeutic agents are systematically presented in Table 5, which categorizes the drugs/ligands by year and first author.

Novel therapeutic strategies that focus on these targets encompass nanomaterial-based systems like Oxa@Mil-100(Fe). This system integrates oxaliplatin chemotherapy with Fe3+-induced glutathione depletion and the Fenton reaction to generate ROS, effectively enhancing both apoptosis and ferroptosis [60]. In a similar vein, MSN-CUR@CM nanoparticles promote ferroptosis by increasing levels of heme oxygenase-1 (HO-1) and decreasing *GPX4*, while their cancer cell membrane coating improves targeting to tumors [65]. The field of immunotherapy is rapidly evolving, with methods such as GPX4-overexpressing NK-92 cells that can mitigate L-KYN-induced ferroptosis within the tumor microenvironment, thus revitalizing anti-tumor immune responses [52]. Additionally, LLI liposomes, when used alongside photodynamic therapy and Liproxstatin-1, work to prevent neutrophil ferroptosis and boost the effectiveness of anti-PD-1 treatments [79]. New targets are also being identified, including non-coding RNAs and microproteins like *HCP5*-derived 132-amino acid microprotein (*HCP5-132aa*), which is a microprotein from lncRNA that stabilizes *SLC7A11* and *G6PD* mRNA through interactions with *YBX1*/*ELAVL1*, thereby inhibiting ferroptosis [61]. Furthermore, histone deacetylase inhibitors (HDACi) such as vorinostat can induce ferroptosis by modifying lipid peroxidation regulators like *ACSL4* and *POR*, a mechanism that is not influenced by genetic factors [62]. Lastly, zanamivir aims at reversing ferroptosis resistance by targeting the assembly of mitochondrial supercomplexes mediated by *SOX13*/*SCAF1* [63]. A comprehensive overview of these ferroptosis-targeting agents, including their mechanisms of action and year of discovery, is provided in Table 5.

Targeting ferroptosis in GC encompasses several distinct areas. Key targets include metabolic regulators, such as *GPX4* and *SLC7A11*, and redox sensors, including *NRF2* and *NOX4*. Furthermore, strategies involve immune system modulators,

Table 5. Drug/Ligand and Target/Pathway of Ferroptosis in Gastric Cancer.

Year	First Author	Country	Target/Pathway	Drug/Ligand
2021	Liying Zhao [40]	China	*GPX4*	Apatinib
2021	Shunhong Mao [41]	China	miR-489-3p/*SLC7A11*	Levobupivacaine
2021	Ying Liu [42]	China	*GPX4*	a2 (JDA derivative)
2021	Jing Wang [43]	China	twist1	CPEB1
2021	Dazhi Fu [22]	China	Nrf2/Keap1/xCT	ATF3
2022	Mingjie Xia [44]	China	GSH	mPEG-PLG (DNs)
2022	Zhian Chen [45]	China	PTT	PP@Mn NPs
2022	Ke Chen [46]	China	Rev-erbα	Arenobufagin (ArBu)
2022	Tingan Wang [47]	China	p62-Keap1-Nrf2	LTBP2
2022	Jinping Zhang [48]	China	GSH	6-TG
2022	Rongrong Li [49]	China	*GPX4*; *NOX4*; PTGS2	XN4
2022	Guoquan Huang [50]	China	*FBXW7*	*BDNF-AS*
2022	Yang Ye [51]	China	*BAP1-IP3R*	DIM
2023	Jianxin Cui [52]	China	IDO	L-kynurenine
2023	Xiang Gao [53]	China	hsa_circ_0008035/*miR-302a*/*E2F7*	DEX
2023	Fang Zheng [54]	China	*NRF2*/ETH1	Polyphyllin I
2023	Wenshuai Zhu [55]	China	ALOX5	PHKG2
2023	Baoxinzi Liu [56]	China	COL12A1	JYQHD
2023	Hongwei Wang [57]	China	RT	MON@PG
2023	Fang Zheng [58]	China	miR-124-3p	Polyphyllin I
2023	Fengying Tang [59]	China	miR-496/ATF2	Amentoflavone
2024	Boyao Sun [60]	China	GSH	Oxaliplatin-Loaded Mil-100 (Fe)
2024	Danping Sun [38]	China	PD-L1	Simvastatin
2024	Qiuhui Li [61]	China	*HCP5-132aa*	Cas9/sgRNA-A AV
2024	Yanmei Peng [39]	China	CagA	Apatinib
2024	Robert Jenke [62]	Germany	HDAC	Class I HDACi (VK1, entinostat)
2024	Hui Yang [63]	China	*SOX13*	Zanamivir
2024	Yi Lu [33]	China	GSH	Myricetin
2024	Xiaoqing Guan [64]	China	*USP7*	DHPO
2024	Yuanyuan Fan [65]	China	HO-1; *GPX4*	MSN-CUR@CM
2024	Sujuan Xi [66]	China	*SLC7A11*; *GPX4*	Chrysophanol
2025	Nan Yan [67]	China	Nrf2/GGTLC2	Crocin
2025	Junjing Zhang [68]	China	*OTUD5*	Nutlin-3a
2025	Yan Niu [69]	China	*STX1A*	Knock down
2025	Yue Zou [70]	China	SIRT3	TAS
2025	Yangwei Xu [71]	China	WTX_L/β-arrestin2/*LCN2*	WTX
2025	Yiying Wang [72]	China	*DLEU1*/*mTOR*/*GPX4*	Shikonin
2025	Qianqian Zhao [73]	China	*GPX4*	TRNC@P + L
2025	Huayang Yu [74]	China	c-Fos/*SREBF1*	Alkannin
2025	Luzhou Xu [75]	China	GSH	OD-M
2025	Xinyi Dai [76]	China	miR-199-3p/*ACSL4*	QZJWD
2025	Yu Fu [77]	China	*NCOA4*	Salidroside

specifically NK cells and neutrophils within the tumor microenvironment, as well as epigenetic agents like HDAC inhibitors. These targets address the challenges of heterogeneity and treatment resistance in GC. Furthermore, they support combination therapies that integrate chemotherapy, immunotherapy, and nanotechnology. Future studies should focus on patient stratification based on biomarkers and the clinical application of these mechanisms to improve treatment outcomes for this aggressive cancer.

4.4 Drug Molecules Involved in Ferroptosis in GC

Molecules associated with iron and their role in treating GC show considerable potential for enhancing therapeutic outcomes, especially in instances of resistance to immunotherapy and unfavorable prognoses. Research indicates that statins like simvastatin can increase the responsiveness of GC cells to immunotherapy by influencing ferroptosis-related markers such as *SLC7A11* and *GPX4* [38]. The integration of immunotherapy with chemotherapy has emerged as the recommended first-line approach for advanced GC, as endorsed by various guidelines and expert opinions. Evidence

Table 6. Chinese herbal molecules and formulas involved in ferroptosis of gastric cancer.

Drug molecule	Source	Molecular formula	Structure	Description	Target/Pathway	Ref.
Brucine	*Strychnos nux-vomica*		$C_{23}H_{28}N_2O_4$	Alkaloid	*NF-κB*	[80]
Coumarin	Tonka bean		$C_9H_6O_2$	Aromatic organic compounds	*KRAS*	[81]
Baicalin	*Medicago truncatula*		$C_{21}H_{18}O_{11}$	Flavonoids	*SLC7A11/ GPX4/* ROS	[82]
Myricetin	*Myrica nagi*		$C_{15}H_{10}O_8$	Flavonoids	*NOX4*	[33]
Quercetin	*Glycyrrhiza uralensis*		$C_{15}H_{10}O_7$	Flavonoids	*ATG5*	[83]
β-Ionone	*Viola odorata Linn.*		$C_{13}H_{20}O$	Ketones, Aldehydes, Acids	Wnt/*β*-catenin	[84]
Shikonin	*Lithospermum erythrorhizon*		$C_{16}H_{16}O_5$	Naphthalene Quinones	*TLR4*	[81]
Curcumin	*Curcuma longa*		$C_{21}H_{20}O_6$	Phenols	*PI3K/ AKT/ mTOR*	[85]
Magnolol	*Magnolia officinalis*		$C_{18}H_{18}O_2$	Phenylephrineids	*KRAS*	[81]
Resveratrol	Grape		$C_{14}H_{12}O_3$	Polyphenols	*TLR4*	[81]
Curcumin	*Curcuma longa*		$C_{21}H_{26}O_6$	Polyphenols	*TLR4*	[81]
Salvianolic acid B	Samanea saman		$C_{36}H_{30}O_{16}$	Polyphenols	*TLR4*	[81]
Psoralidin	*Psoralea corylifolia* L.		$C_{20}H_{16}O_5$	Polyphenols	*ACSL4*	[86]
Sanguinarine chloride	*Sanguinaria canadensis*		$C_{20}H_{14}ClNO_4$	Pyridine Alkaloids	*SIRT1/NOS2/SOD1*	[87]
Shikonin	*Purple Gromwell*		$C_{16}H_{16}O_5$	Quinones	*DLEU1/mTOR/GPX4*	[72]
Chrysophanol	*Rheum palmatum*		$C_{15}H_{10}O_4$	Quinones	*SLC7A11*; *GPX4*	[66]
Artesunate	*Sophora macrocarpa* Sm.		$C_{19}H_{28}O_8$	Sesquiterpenes	*TFRC*	[88]
Polyphyllin B	*Paris polyphylla*		$C_5H_2O_{21}$	Steroidal Saponins	GPx4; *TFR1*; *NOCA4*; *FTH1*	[89]
Dioscin	*Paris polyphylla rhizomes roots*		$C_{45}H_{72}O_{16}$	Steroids	*SLC7A11/GPX4*	[90]
Periplocymarin	*Periploca sepium*		$C_{30}H_{46}O_8$	Steroids	*ATP1A1*	[91]
Pachynic acid	*Poria cocos*		$C_{33}H_{52}O_5$	Terpenoids	*PDGFRB*	[92]
Celastrol	*Tripterygium wilfordii*		$C_{29}H_{38}O_4$	Terpenoids	*GPX4*; *SLC7A11*	[93]
Dihydroartemisinin	*Sophora macrocarpa*		$C_{15}H_{24}O_5$	Terpenoids	ROS	[75]
Oridonin	*Rabdosia rubescens*		$C_{20}H_{28}O_6$	Terpenoids	GSH	[75]
Dihydroartemisinin	*Sophora macrocarpa*		$C_{15}H_{24}O_5$	Terpenoids	*GPX4*	[94]
Curcumol	*Curcuma phaeocaulis*		$C_{13}H_{24}O_2$	Terpenoids	62/KEAP1/*NRF2*	[95]
Asiaticoside	*Tagetes lucida*		$C_{48}H_{78}O_{19}$	Terpenoids	Wnt/*β*-catenin	[96]
Genipin	*Gardenia jasminoides*		$C_{11}H_{14}O_5$	Terpenoids	*AURKA*; *BCAT2*; *DHODH*	[97]
Tanshinone I	Samanea saman		$C_{18}H_{12}O_3$	Terpenoids	*KDM4D/p53*	[98]
Tanshinone IIA	Salvia Miltiorrhiza		$C_{19}H_{18}O_3$	Terpenoids	*SLC7A11*	[99]
Gambogic acid	*Gamboge*		$C_{38}H_{44}O_8$	Xanthones	miR-1291/*FOXA2*	[100]

Table 7. Chinese herbal formulas and extracts involved in ferroptosis of gastric cancer.

Drug molecule	Source	Molecular formula	Description	Target/Pathway	Ref.
Chinese agarwood petroleum ether extract (CAPEE)	Agarwood	-	-	D1/*CDK4*	[101]
Mori Folium ethanol extracts	Mori Folium	-	-	*PI3K*/*AKT*	[102]
Red ginseng polysaccharide	-	-	-	*PI3K*/Akt	[103]
Poria (PA)	Chinese herbal medicine	-	Chinese medicinal materials	*TNF-β*	[104]
Qizhu Jianwei decoction (QZJWD)	Chinese herbal medicine	*Astragalus membranaceus* (Fisch.) Beg.var.mongholicus (Bge.) Hsiao 30g, *Polygonatum odoratum* (Mill.) Druce 12g, Atractylodis macrocephala Koidz. 10g, *Curcuma phaeocaulis* Val. 10g, Evodia rutaecarpa (Juss.) Benth 1.5g, *Coptis chinensis* Franch. 3g, *Agrimonia Pliosa* Ledeb. 30g, *Rabdosia rubescens* (Hemsl.) Hara 30g, *Salvia chinensis* Benth. 30g, Glycyrrhiza uralensis Fisch. 5g.	Prescription	miR-199-3p/ *ACSL4*	[76]
Fuzheng Nizeng Decoction (FZNZ)	Chinese herbal medicine	Astragalus mongholicus Bunge 15g, *Atractylodes macrocephala* Koidz. 10g, Glycyrrhiza uralensis Fisch. ex DC. 5g, *Citrus* × *aurantium* L. 10g, *Cyperus rotundus* L. 15g, *Panax notoginseng* (Burkill) F.H.Chen 3g, *Pinellia ternata* (Thunb.) Makino 5g, Poria Cocos (Schw.) Wolf. 10g, *Curcuma aromatica* Salisb. 12g, *Salvia miltiorrhiza Bunge* 10g, *Actinidia chinensis* Planch. 15g, *Scutellaria barbata* D. Don 15g and *Solanum lyratum* Thunb. 15g.	Prescription	*GPX4*/GSH	[105]
Yi-qi-hua-yu-jie-du decoction (YJD)	Chinese herbal medicine	Astragalus mongholicus Bunge 15g, *Codonopsis pilosula* (Franch.) Nannf 15g, Citrus × acida Pers 6g, Pinellia tuberifera Ten 10g, *Poria cocos* 10g, *Aucklandia costus* Falc 6g, *Wurfbainia uliginosa* (J.Koenig) Giseke 3g, Atractylodes macrocephala Koidz 10g, *Paeonia lactiflora* Pall 10g, *Angelica sinensis* (Oliv.) Diels 10g, *Sparganium stoloniferum* (Buch.-Ham. ex Graebn.) 10g, Buch.-Ham. ex Juz. *Curcuma aromatica* Salisb 10g, Salvia chinensis Benth 30g, *Scleromitrion angustifolium* (Cham. Schltdl.) 30g, Benth, *Glycyrrhiza glabra* L 5g.	Prescription	*AKT*/ GSK3*β*/ *NRF2*/ *GPX4*	[106]
Shuangshu Decoction (SSD)	Chinese herbal medicine	Bran-fried Atractylodes rhizome 20g, Atractylodes macrocephala 20g, *Dendrobium* 15g, ginger-processed Pinellia tuber 10g, *Poria cocos* 15g, aged tangerine peel 10g, Magnolia officinalis 10g, raw chicken gizzard membrane 15g, medicated leaven 15g, Sichuan chinaberry 10g, fried malt 15g, charred hawthorn 15g, Corydalis yanhusuo 10g.	Prescription	P53/ *SLC7A11*/ *GPX4*	[107]
Weifuchun (WFC)	Chinese herbal medicine	Ferulic acid, Dibutyl terephthalate, Caffeic acid, Quercetin, Lariciresinol, Hesperetin, Glauocalyxin A, beta-sitosterol, Melissoidesin U, naringenin, Pomiferin F, nobiletin, Angustifolin, Dioctyl Phthalate, Glauocalyxin B, (6Z, 10E, 14E, 18E)- 2, 6, 10, 15, 19, 23 -hexa -methyltetra-cosa-2, 6, 10, 14, 18, 22-hexaene, Melissoidesin O, ginsenoside rh2.	Chinese patent medicine[a]	KEGG	[108]
Jian Yun Qing Hua Decoction (JYQHD)	Chinese herbal medicine	*Pseudostellaria heterophylla* (Miq.) Pax (Tai zi shen) 15g, Astragalus membranaceus (Fisch.) Bunge (Huang qi) 30g, Atractylodes macrocephala Koidz. (Bai zhu) 30g, *Dioscorea polystachya* Turcz. (Shan yao) 30g, *Coix lacryma-jobi* L. (Yi yi ren) 45g, *Salvia miltiorrhiza Bge*. (Dan shen) 15g, *Curcuma phaeocaulis Valeton* (E zhu) 10g, Citrus aurantium L. (Zhi shi) 10g, *Bupleurum chinense* DC. (Chai hu) 10g, *Hedyotis diffusa* Willd. (Bai hua she she cao) 30g, *Scutellaria barbata* D.Don (Ban zhi lian) 30g, *Lobelia chinensis* Lour. (Ban bian lian) 30g, *Paris polyphylla* Sm. (Chong lou) 15g.	Prescription	COL12A1	[56]

suggests that re-administering immune checkpoint inhibitors can yield clinical advantages for patients with advanced GC, while maintaining manageable safety profiles [109]. For patients with unresectable locally advanced or metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-negative GC, the combination of chemotherapy and immunotherapy has established itself as the new first-line treatment standard. Nonetheless, the outlook for patients remains grim. Against this clinical backdrop, fruquintinib, a highly selective multi-target receptor tyrosine kinase inhibitor, has demonstrated promising efficacy and an acceptable safety profile in advanced GC [110]. Similarly, tislelizumab combined with paclitaxel-based chemotherapy regimens has shown high response rates, extended survival, and a favorable

safety profile [111]. Notably, it has been demonstrated that chemotherapeutic agents such as cisplatin and paclitaxel can modulate ferroptosis-related signaling in GC cells, for instance by activating the *USP7/hnRNPA1* pathway to regulate *miR-522* release and thereby influence lipid ROS accumulation [36], underscoring the mechanistic interplay between standard chemotherapy regimens and ferroptosis pathways in the tumor microenvironment. Many first-line drugs for GC can induce anti-tumor activity by facilitating ferroptosis; however, their clinical use is frequently hindered by significant side effects and drug resistance. With the rise of ferroptosis research, there has been a growing interest in utilizing traditional Chinese medicine (TCM) to regulate ferroptosis for GC treatment. Numerous studies have shown that TCM compounds can effectively inhibit the growth, migration, and spread of GC while minimizing side effects. We have compiled lists of specific TCM compounds and formulas that play a role in regulating ferroptosis for GC therapy in Table 6 and Table 7, offering patients more diverse and effective treatment options.

5 Conclusion and Prospects

Ferroptosis represents a specific type of regulated cell death (RCD) that is marked by the accumulation of lipid peroxides in an iron-dependent manner, setting it apart from conventional cell death mechanisms like apoptosis and pyroptosis. The process is driven by the combined disruption of three essential networks: iron metabolism, lipid metabolism, and the balance of ROS. This study adopts bibliometric analysis to explore the global research trends of ferroptosis in gastric cancer, and systematically reviews the underlying mechanism of ferroptosis in the occurrence and progression of gastric cancer. It organically combines bibliometric analysis with narrative review to further clarify the relationship between gastric cancer and ferroptosis. Despite the comprehensive nature of this bibliometric study, several limitations must be acknowledged. First, the data source was restricted to the Web of Science Core Collection. While this is a premier database, excluding other reputable databases such as PubMed, Scopus, or Embase may have resulted in the omission of relevant studies, potentially introducing selection bias. Second, the analysis was limited to English-language publications. Given the high incidence of gastric cancer in East Asia, significant research output in Chinese or Japanese journals may have been underrepresented, skewing the geographical distribution of contributions. Third, bibliometric indicators such as citation counts and impact factors, while useful for measuring academic influence, do not necessarily equate to clinical efficacy or translational success. High citation counts may reflect controversy or methodological critique as much as groundbreaking discovery. Therefore, it does not evaluate the quality of individual studies or the reproducibility of specific experimental findings regarding ferroptosis mechanisms in GC. Future research should prioritize the translation of basic mechanistic discoveries into clinical applications. While the molecular regulators of ferroptosis (e.g.*GPX4*, *SLC7A11*) are well-characterized in vitro, their validation in large-scale clinical cohorts remains limited. There is an urgent need for clinical trials evaluating the safety and efficacy of ferroptosis-inducing agents, either as monotherapies or in combination with standard chemotherapy and immunotherapy. Furthermore, given the heterogeneity of gastric cancer, future studies should focus on identifying biomarkers that predict patient sensitivity to ferroptosis, thereby enabling personalized medicine approaches. Finally, overcoming the challenge of drug delivery to specifically target tumor cells while sparing normal tissues remains a critical hurdle that requires innovative nanotechnology-based solutions. From a technical standpoint, the methods for measuring LIP content and PUFA-PL levels in GC tissues, including in situ imaging and lipidomics, have not been widely implemented, which complicates the accurate evaluation of ferroptosis.Subsequent studies need to concentrate on clarifying the regulatory mechanisms that lead to ferroptosis in GC, formulating more targeted combination inhibitors, initiating multicenter clinical trials, confirming the effectiveness of biomarkers and inducers related to ferroptosis, designing advanced detection methods for ferroptosis, and setting up a comprehensive system for the mechanism-detection-treatment framework.

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