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REVIEW

The Current Situation and Future Trends of Ergothioneine in Biology and Medical Research: A Bibliometric Analysis

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Background: Ergothioneine (EGT) is a natural antioxidant with multiple cellular protective properties. Recently, due to the improvement of production efficiency, EGT-related products have been more widely used. This paper studies the present situation of global research trends and hotspots of EGT to better grasp the direction of EGT research in biology and medical.

Methods: We searched for relevant literature on EGT in the Web of Science Core Collection (WOSCC) and SciFinder databases on August 16, 2025. CiteSpace, VOSviewer, Tableau Desktop, Microsoft Excel, Bibliometrix program package and Biorender software are used for statistical analysis and visualisation.

Results: A total of 800 articles were collected. It is found that the average growth rate of EGT's publications in biology and medicine from 1996 to 2025 was 17.33%. Based on the statistical results by country/region, it is evident that the primary focal areas of research activity within this domain exhibit concentrated distribution across the Americas, Asia, and Europe. Among the top ten authors in terms of publication volume, six are from Asia, three are from Poland in Europe, and one is from the United States (USA) in the Americas. The highest H-index ranking author is Halliwell B (169).

Conclusion: Based on the keyword visualisation results, the current research hotspots are mainly divided into three clusters: 1) The absorption, distribution, anti-inflammatory and antioxidant biological molecular mechanisms of EGT in vivo. 2) The impact of EGT's antioxidant and anti-inflammatory effects on various diseases; 3) The source of EGT, the antioxidant potential of edible fungi in vitro, and its influencing factors. At present, research on EGT in biology and medicine mainly focuses on basic theories, so we believe that clinical trial research will become a hot trend in the future.

Keywords: ergothioneine, bibliometric analysis, mushroom, fungi, health

Introduction

Ergothioneine (EGT) is an antioxidant present in food, first isolated by Tanret C from the ergot fungi Claviceps purpurea in 1909, hence its name.[1] Subsequently, Barger G and Ewins AJ proved that it is a derivative of histidine (2-mercaptohistidine trimethylbetaine).[2] EGT is widely present in natural foods (mainly in some fungi and bacteria), and cannot be synthesised by humans and animals. However, the organic cation transporter (OCTN1) can specifically and effectively absorb EGT from the daily diet, and accumulate EGT in tissues and organs of humans and other animals. The concentration of EGT in tissues is positively correlated with the distribution of OCTN1.[3,4] EGT is a tautomer with two forms: thione and thiol. EGT mainly exists in the form of thione and has a high oxidation-reduction potential. Therefore, EGT is considered to have stronger antioxidant capacity than other thiols, making it a very effective antioxidant and cell protector, and possessing metal chelating properties.[5–8]

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In previous studies, researchers have discovered various cellular protective properties of EGT, such as anti-inflammatory, radiation protection, and antioxidant properties.[9–12] Scholars used human neuronal hybridoma cells, human alveolar epithelial cells, rat chromaffin cells, and other cells as samples. The results show that EGT can reduce oxidative damage to cellular DNA in vitro, inhibit tumour necrosis factor-α (TNF-α) induced nuclear factor kappa-B (NF-κB) activation and interleukin-8 (IL-8) release in alveolar epithelial cells, and weaken amyloid protein (Abeta) induced cell apoptosis.[13–15] Yang et al[16] orally administered EGT (0.5 or 2 mg/kg body weight) to mice for 16 days and injected Abeta into the hippocampus of mice. It was found that EGT could significantly prevent the accumulation of Abeta and brain lipid peroxidation in the hippocampus of mice. In long memory avoidance and water maze tests, the results showed that oral EGT could significantly reduce escape latency and increase the frequency of successful avoidance. Based on previous basic research results, EGT is considered to have great therapeutic potential for neurodegenerative diseases, aging, cardiovascular disease, and inflammation. Due to the difficulty of synthesis and extraction, the price of EGT has always been very expensive in the past. This is one of the reasons that constrain the development of EGT. In recent years, with the completion of synthesis technology, the price of EGT has decreased. The European Union, the United States, Canada, and Japan have successively issued licenses and standards for the use of EGT in the fields of food, medicine, cosmetics, etc. China has also included it in the list of raw materials for cosmetics. Therefore, we believe that EGT will become a research hotspot in the coming years.

However, currently EGT does not apply in clinical treatment because its research is not yet mature. Firstly, the targets, bioavailability, and metabolic pathways of oral EGT are not fully understood. Recently, it was reported in *CELL METABOLISM* that 3-mercaptoacetate sulfatase (MPST) is a direct molecular target of EGT, which can improve mitochondrial respiration and exercise training performance in mice by binding and activating MPST. Nonetheless, current research on the mechanism of EGT is still incomplete. Secondly, there is a lack of sufficient clinical data, which is related to the incomplete mechanism research mentioned in the first point. Yau's pilot study results showed that long-term use of EGT is safe and may have the potential to delay cognitive decline in the elderly.[17] Ishimoto's[18] experimental results showed that EGT can improve human cognitive function, but the sample size was only 48 cases. Obviously, the sample size for clinical research on EGT is insufficient and in the early stages of the experiment. Thirdly, compared to the huge industrial demand, the preparation of EGT still needs further improvement. EGT mainly relies on natural product extraction, chemical synthesis and biosynthesis. Currently, biosynthesis technology has increased fermentation efficiency by 15 times compared to traditional methods. However, further research and improvement are needed on how to meet the growing market demand, control costs, improve purity, and avoid toxic substances in the production process. EGT undoubtedly has great therapeutic potential in the field of biomedicine. Although there have been some studies, the current research on EGT is still immature. As mentioned above, currently in the fields of biology and medicine, the research direction of EGT targets, hot topics in clinical trials, and research trends in synthetic processes are not clear. Therefore, a systematic literature review is needed to identify existing research progress and predict future research directions.

Bibliometrics is a method of literature analysis in which researchers can use specific software to create knowledge maps and predict future frontiers to showcase the evolution of a particular field of knowledge.[19–21] The bibliometric analysis methodology enables a systematic examination of the interconnected dynamics among authors, institutions, countries, and journals within specific academic disciplines.[22,23] Bibliometrics can not only identify existing trend, but also determine further scope and inspire future research.[24] To determine the current research centers, hotspots, and future research trends in this field, a bibliometric analysis is conducted for publications related to EGT and medicine published in the WOSCC and SciFinder database before August 2025.

Methods

Data Sources and Retrieval Strategies

EGT is a chemical substance that has received widespread attention in the field of biomedicine. A large number of relevant studies, which have been included in SciFinder and WOSCC databases, are chosen for literature retrieval. All data was collected on August 16, 2025. The search strategy in the WOSCC is "(TS=(Ergothioneine OR 2-Thiol-L-histidine-betaine OR 2 Thiol L histidine betaine thioneins)) AND (TS=. (biolog* OR dietary OR nutri* OR disease* OR health* OR medic* OR pharmac* OR life*))”. All articles in the sub-databases have been included. Articles or reviews are selected as the literature type. Language is not limited. In the SciFinder database, we retrieved the Chemical Abstracts Service Registry Number (CAS) 497–30-3 of EGT and obtained 2709 articles. Based on this, we restricted the words “diet”, “nutrition”, “nutrient”, “disease”, “diseases”, “healthy”, “medical”, “medicine”, “pharmacology”, “pharmacognosy”, “life”, “biology”, “biological”. Choose journal and review as the article types. The time limit for both databases is between 1996 and 2025. After overlaying and removing duplicate records and incomplete literature from two databases, we finally obtained 800 articles. The detailed process is shown in Figure 1.

Inclusion and Exclusion Criteria

Inclusion criteria: ① Literature related to EGT in biology and medicine; ② Research papers or review papers.

Exclusion criteria: ① Papers with incomplete bibliography; ② Papers unrelated to the topic; ③ Meeting abstract, letter, editorial material, correction, early access, proceeding paper, book chapters, data paper, news item, duplicate records, retracted publication, etc.

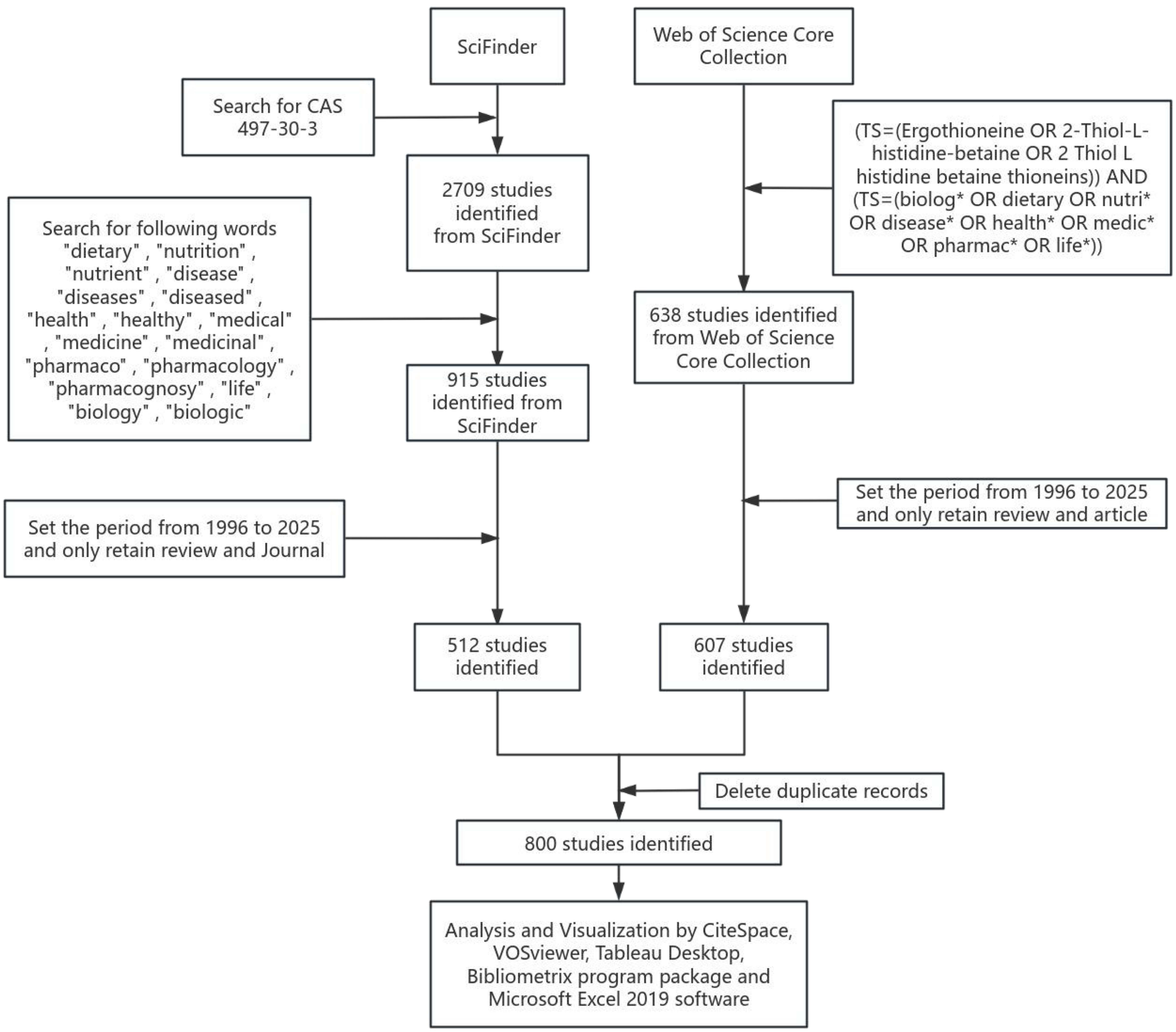

Figure 1 Flowchart for including studies to review.
Abbreviation: CAS, Chemical Abstracts Service Registry Number.

Data Analysis and Statistics

The country/region, institution and author are analysed using CiteSpace (V.6.3.R3) software.[25] VOSviewer (version 1.6.20) is used for visualising bibliometric networks, such as keyword hotspots and cluster analysis.[26,27] Microsoft Excel 2019 software is used to analyse annual publication trends. Country/region, distribution is visualised using Tableau Desktop. Visualized EGT's publications in biology and medical research using the Bibliometrix program package.[28] The drawing of the mechanism diagram was done using Biorender software (version 5.0).

The analysis indicators include the number of publications, average citation count per publication, country/region, institution, author and keywords. In a network diagram, distinct nodes represent various entities, including institutions, countries/regions, and authors. Whether presented in CiteSpace or VOSviewer, the larger the circle, the greater the corresponding quantity in the network visualisation.[27] In the visualisation network diagram of CiteSpace, the colour of each circle corresponds to a different year, representing the publication year of the article. Centrality embodies the significance of a node within a knowledge network and its influence on other interconnected nodes.[25,29] We are preparing to create a knowledge map and visualise the research status, trends, collaborations, and emerging hotspots in this field.

Results

EGT's Publishing Trend in Biology and Medical Research

A total of 800 papers met the inclusion criteria, including 687 (85.88%) research articles and 113 (14.13%) review articles. It has been observed that the number of publications and citation frequency have shown an overall increasing trend year by year, with an average growth rate of 17.33% from 1996 to 2025 (R^2 = 0.9656). Up to the search date, these publications have been cited 23942 times, with an average of 29.93 citations. From 1996 to 2025, the average annual citation count in this field has shown a rapid upward trend overall. The detailed information is shown in Figure 2.

Distribution of Country/Region

When we set the "node type" to "country/region", publications are distributed in 79 countries/regions, as shown in the country/region network map (Figure 3A) (Figure S1). China has the highest number of publications (215), followed by

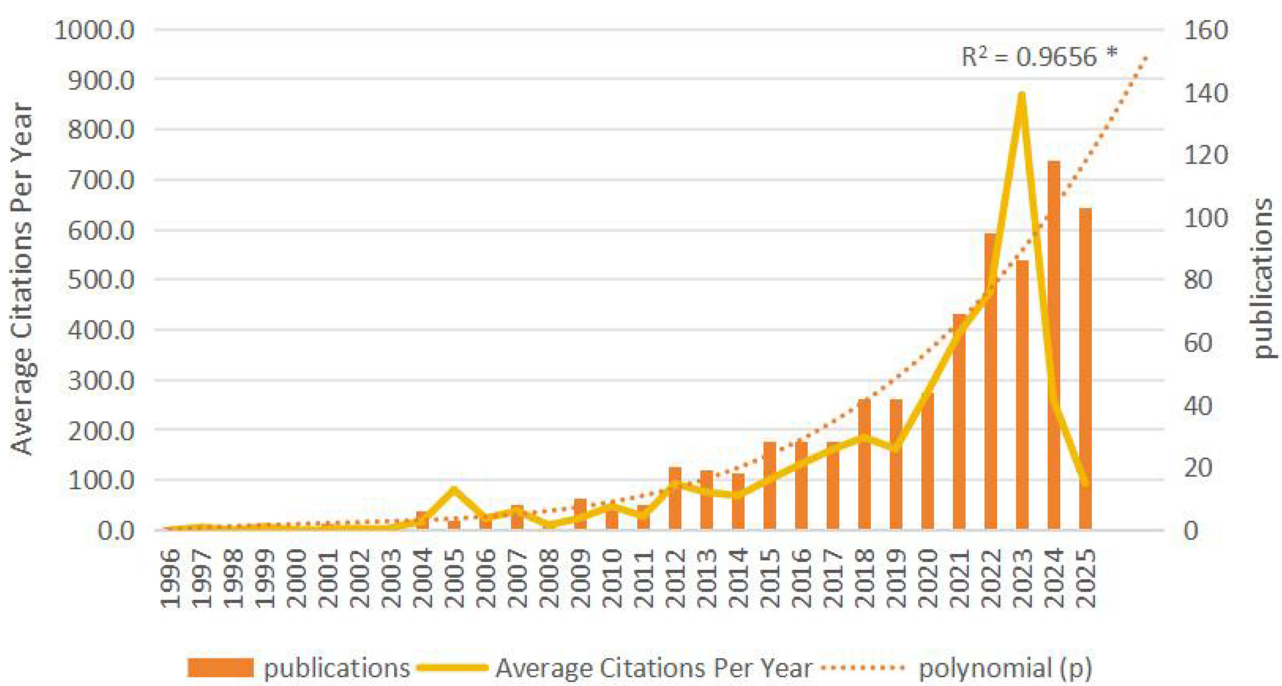

Figure 2 The number of publications and citation frequency of EGT in biology and medical research. *: the R^2 value shows how well the trendline fits the data. It is a statistical measure that ranges from 0 to 1, where 1 indicates a perfect fit. The higher the R-squared value, the better the trendline matches the data points.

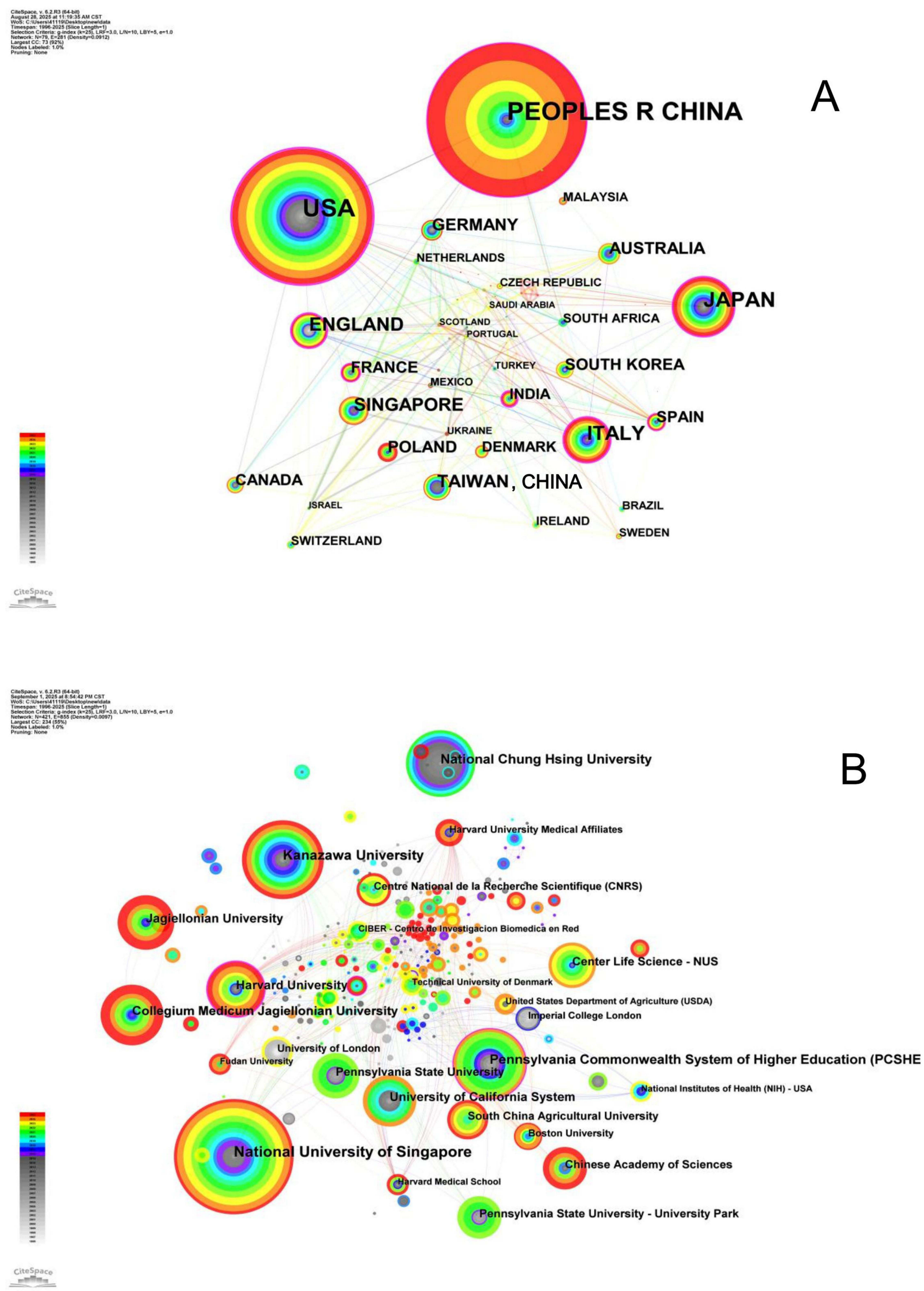

Figure 3 Visualisation of countries/regions and institutions using CiteSpace software. (**A**) Network visualisation map between 79 countries/regions. (**B**) Visualisation diagram of institutional network.

the USA (190), Japan (82), and Italy (62). The countries/regions with high intermediate centrality are the USA (0.44), England (0.34), Japan (0.29), India (0.22), and Italy (0.21). When setting the "Node Type" to "Institution", the results show that 421 institutions have published in biology and medical research of EGT, as shown in the network diagram of the institutions (Figure 3B) (Table 1). The National University of Singapore (38) has the highest frequency of publication, followed by Kanazawa University (26) and Pennsylvania Commonwealth System of Higher Education (PCSHE) (23) (Table 2).

Table 1 Top 10 Countries/Regions Ranked by Number of Publications

Country/Region	Frequency of Publications	Centrality
China	215	0.14
The United States	190	0.44
Japan	82	0.29
Italy	62	0.21
England	47	0.34
Singapore	40	0.03
Taiwan, China	37	0.06
Australia	30	0.04
Germany	29	0.09
Poland	27	0.00

Note: Sort by publication volume.

Table 2 Top 10 Institutions Ranked by Number of Publications

Institution	Country/Region	Frequency of Publications	Centrality
National University of Singapore	Singapore	38	0.07
Kanazawa University	Japan	26	0.06
Pennsylvania Commonwealth System of Higher Education (PCSHE)	The United States	23	0.17
National Chung Hsing University	Taiwan, China	22	0.00
Collegium Medicum Jagiellonian University	Poland	20	0.00
Jagiellonian University	Poland	18	0.00
Harvard University	The United States	18	0.33
University of California System	The United States	17	0.04
Center Life Science - National University of Singapore	Singapore	15	0.00
Pennsylvania State University	The United States	15	0.00

Note: Sort by publication volume.

Highly Influential Author

We analyze the situation of authors in this field through network diagrams and “Three Field Plots”, as network diagrams can effectively display the author’s publication status. “Three Field Plot” is a commonly used analysis method that helps us better understand data by visualizing three related fields in the same plot. For example, in this article, the three related fields are authors, keywords, and countries/regions (Figure 4A). The results show a total of 4346 authors participated in the research of EGT in biology and medical research (Figure 4B). From the results of the network graph and Three Field Plot, it can be seen that Halliwell B is the scholar with the most publications, having published 28 papers, followed by Kato Y (23) and Mau JL (22). Halliwell B is also the author with the highest citation count and H-index. Overall, the level of collaboration between authors is not close, with a network density of 0.0016. Through the author’s network graph and Three Field Plot, we have summarized the top 10 authors in terms of publication frequency, including their countries/regions, institutions, citation frequency, H-index, centrality, and main research directions (Table 3).

Highly Cited Literature on EGT in Biology and Medical Research

The citation rate of an article has always been an indicator of concern for scholars, and high citation rates often indicate that this type of direction is highly regarded. We analysed the highly cited literature on EGT in biology and medical research using VOSviewer software (Figure S2). The titles, first authors, publication years, journals, impact factors (IF), citation frequencies, and article types of the top 5 articles in terms of citation volume are shown in Table 4.

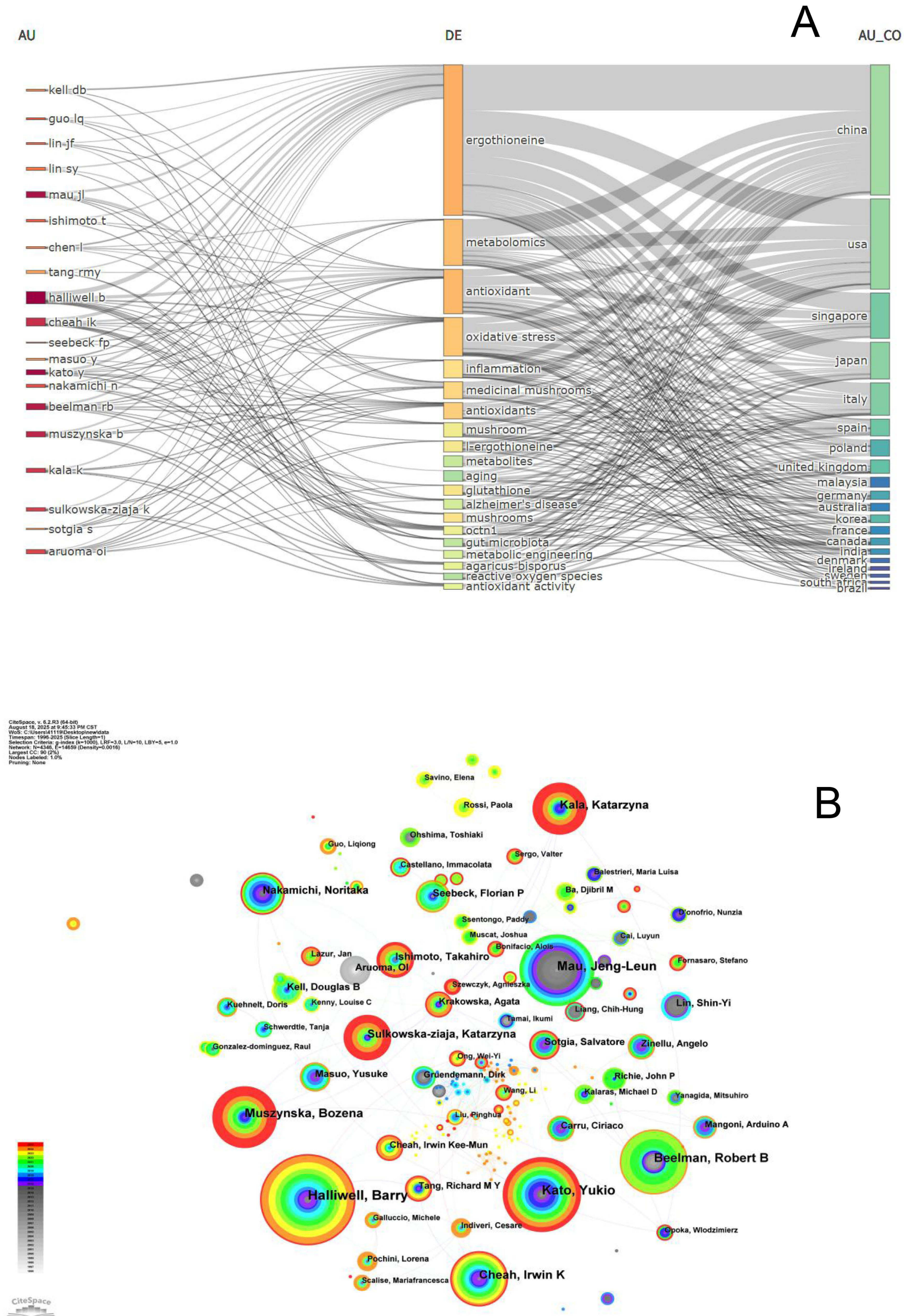

Figure 4 Visual analysis of high impact authors. (**A**) Three Field Plot analysis of authors, keywords, and countries/regions, with the author on the left, keywords in the middle, and country/region on the right. (**B**) Author network visualisation.

Table 3 Basic Information of the Top 10 Authors in Terms of Publication Volume

Authors	Country/Region	Institution	Frequency	Total Citation	Average Citation per Paper	H-Index	Centrality	Main Research Directions
Halliwell B	Singapore	National University of Singapore	28	1842	65.79	169	0	Study the antioxidant capacity and mechanism of EGT, including its effects on human cellular aging and mitochondrial function.[9,11,30–32]
Kato Y	Japan	Kanazawa University	23	580	25.22	45	0	Study on the transport channel OCTN1 of EGT and the antioxidant and anti-aging biological mechanisms of EGT.[33–36]
Mau JL	Taiwan, China	National Chung Hsing University	22	582	26.45	51	0	Study the biological activity of various fungi and the factors affecting their antioxidant capacity.[37–41]
Beelman RB	The United States	Penn State University	20	935	46.75	31	0	Study the effects of EGT (mainly mushrooms) in diet, including the extraction and intake of EGT.[42–46]
Muszynska B	Poland	Jagiellonian University	19	375	19.74	28	0	Study the physiological activity of different parts of various fungi.[47–50]
Cheah IK	Singapore	National University of Singapore	17	1379	81.12	26	0	Study the antioxidant and anti-inflammatory potential, physiological functions, and role of EGT in diseases.[11,31,51–53]
Kala K	Poland	Jagiellonian University	16	239	14.94	18	0	Study the physiological activity of different parts of various fungi.[48,50,54,55]
Sułkowska-Ziaja K	Poland	Collegium Medicum Jagiellonian University	14	144	10.29	23	0	Study the biological components and medicinal value of various fungi.[56–58]
Nakamichi N	Japan	Takasaki University of Health and Welfare	13	297	22.85	28	0	Study the various functions of OCTN1 transport channel in EGT[35,59–61]
Ishimoto T	Japan	Kanazawa University	11	222	20.18	12	0	Study the transport channels, distribution, and functions of EGT in the body[18,62,63]

Note: Sort by publication volume.
Abbreviations: EGT, Ergothioneine; OCTN1, Organic cation transporter.

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Table 4 Top 5 Articles with the Highest Citation Count

Title	First Author	Year	Journal	Impact Factors (Average 5 years)	Citation	Document Type
Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging	Jomova K	2023	*Archives of Toxicology*	6.4	1163	Review
Phenolics as potential antioxidant therapeutic agents: Mechanism and actions	Soobrattee MA	2005	*Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis*	2.1	1100	Article
Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases	Chen Y	2023	*Nature Genetics*	37.4	502	Article
Discovery of the ergothioneine transporter	Gründemann D	2005	*Proceedings of the National Academy of Sciences of the United States of America*	10.6	455	Article
Ergothioneine; antioxidant potential, physiological function and role in disease	Cheah IK	2012	*Biochimica et Biophysica Acta-Molecular Basis of Disease*	5.5	373	Review

Note: Sort by citation count.

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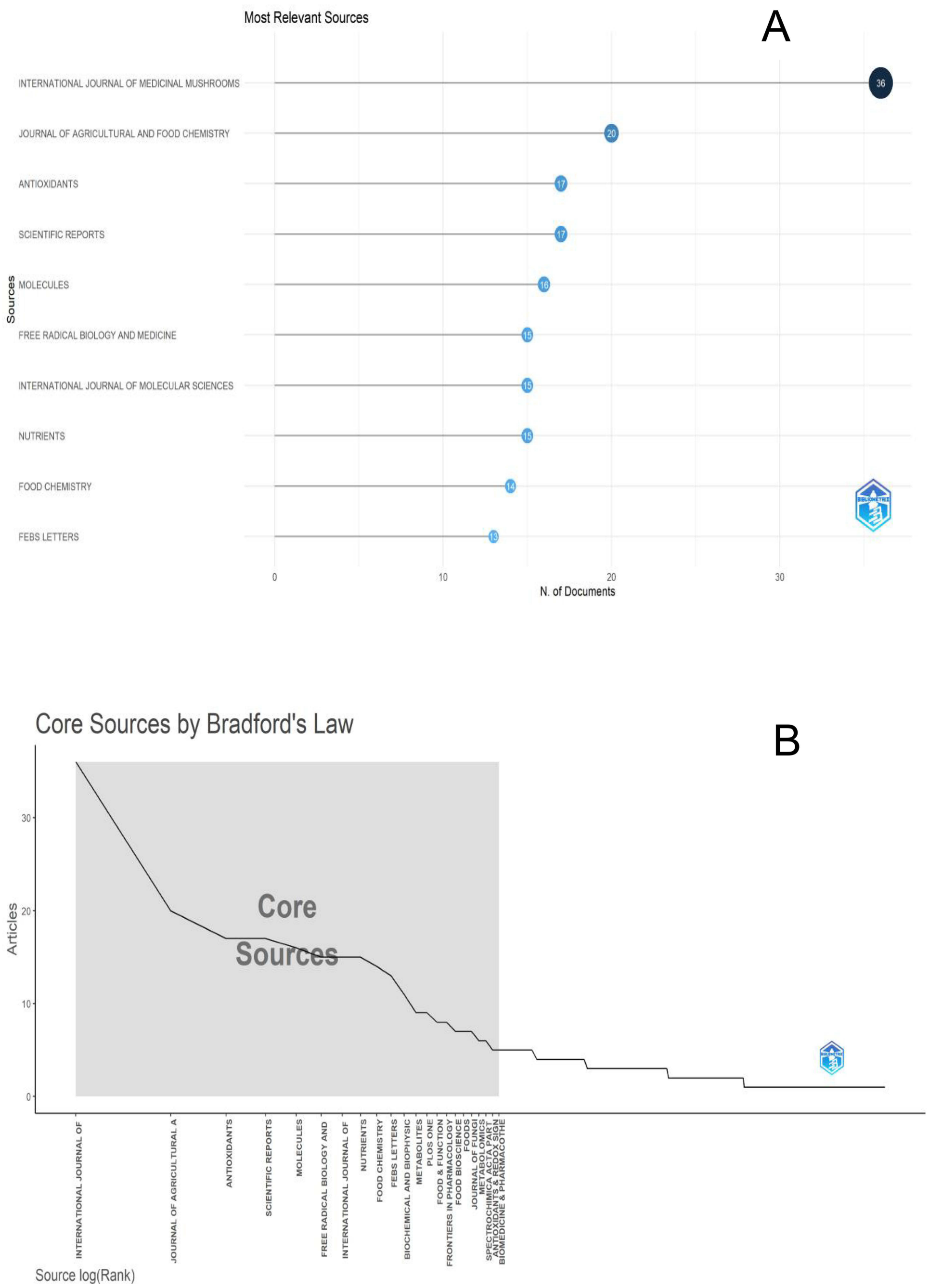
Analysis of Journals

We analysed the publications on EGT in biology and medical research sciences using the Bibliometrix program package (Figure 5). A total of 369 journals published articles related to EGT, with the most prolific being the *INTERNATIONAL JOURNAL OF MEDICINAL MUSHROOMS* (36), which primarily reports research and practices in the medicine-pharmacy field, followed by *JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY* (20), *ANTIOXIDANTS* (17) and *SCIENTIFIC REPORTS* (17). (Figure 5A). According to Bradford's Law, 22 journals contributed one-third of the total publications, as detailed in Figure 5B. The results in Figure 5C show the publication volume of the top 10 publications over the years. From the results, it can be seen that *FREE RADICAL BIOLOGY AND MEDICINE, INTERNATIONAL JOURNAL OF MEDICINAL MUSHROOMS*, and *JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY* are the three journals that published



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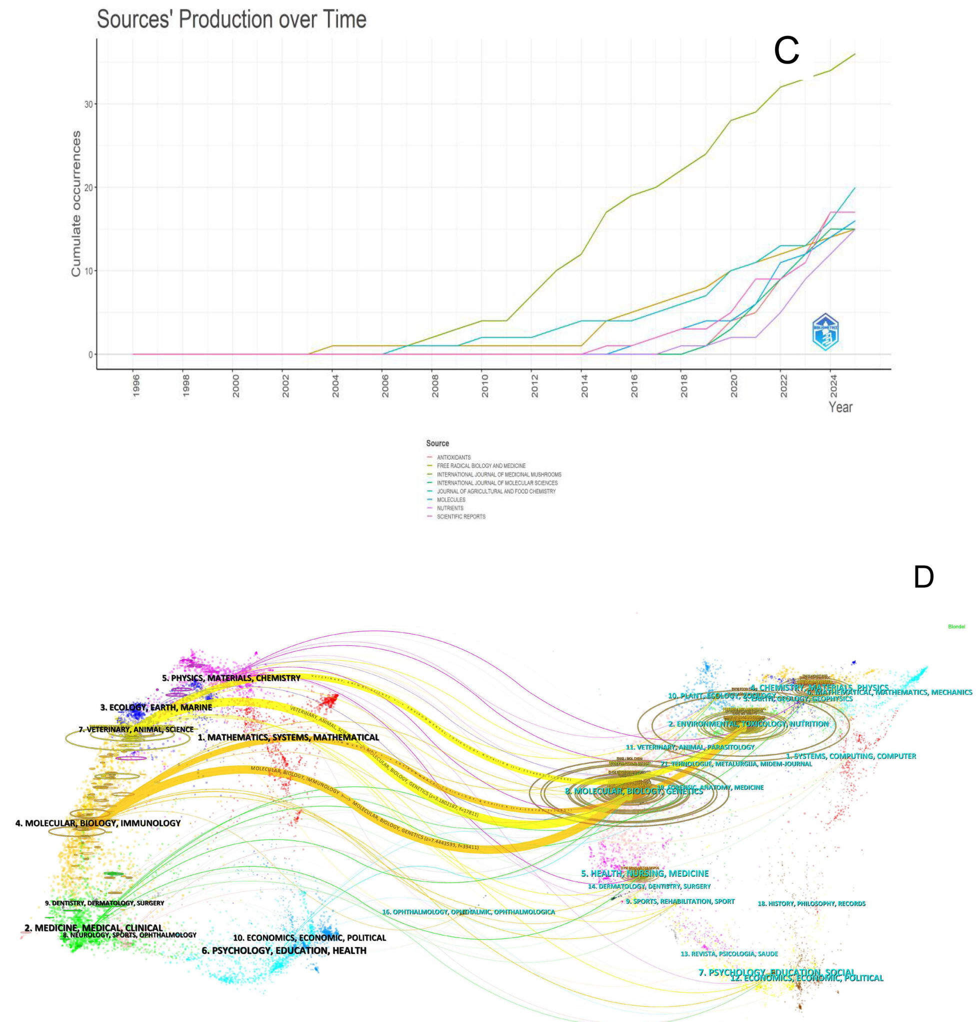


Figure 5 Visual analysis of journals. (**A**) EGT's publications in biology and medical research. (**B**) Core sources analysis based on Bradford's Law. (**C**) Sources' Production Over Time. (**D**) Visualization of EGT citation trends in biology and medical research using a double-layer overlay. The more papers published in a journal, the longer the vertical axis of the ellipse in the graph, and the more authors there are, the longer the horizontal axis of the ellipse.

literature in this field earlier, while the rest of the literature has been extensively published since 2014. The dual-map overlay function in CiteSpace visually delineates the domain-specific distribution of citation patterns by tracing their reference trajectories. In the visualization, the left cluster represents the subject categories of the citing literature, while the right cluster indicates the categories of the cited references.[64] The citation trajectories are distinguished by the colors of their citation zones, and the thickness of these trajectories is proportional to the citation frequency (Z-score-scaled), as shown in Figure 5D. Table 5 summarizes the four major citation trajectories.

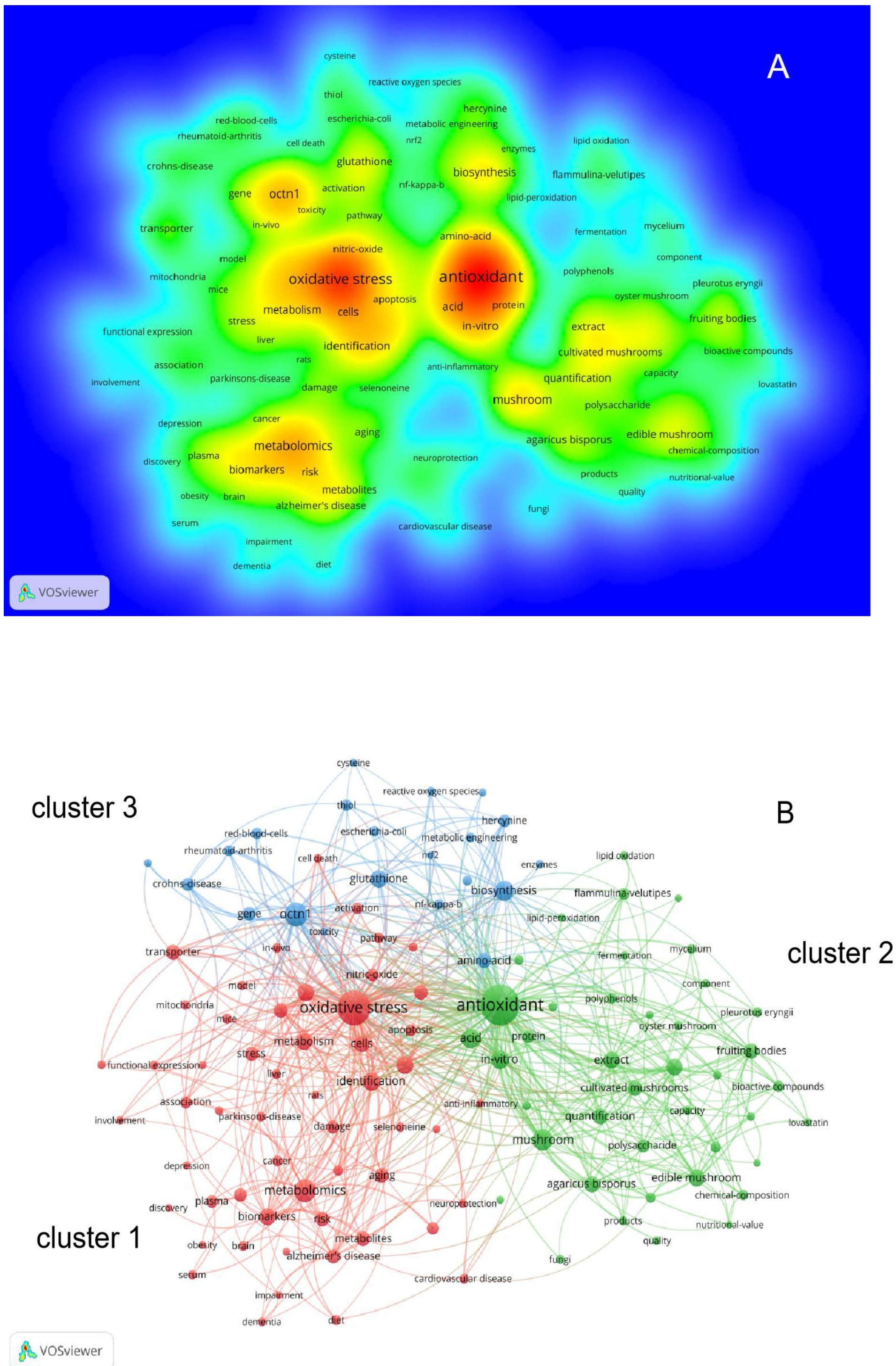
Table 5 The Citation Trend of EGT in Biology and Medical Research

Citing Region	Cited Region	Z-score
Molecular, biology, immunology	Molecular, biology, genetics	7.44
Veterinary, animal, science	Molecular, biology, genetics	3.18
Molecular, biology, immunology	Environmental, toxicology, nutrition	2.22
Veterinary, animal, science	Environmental, toxicology, nutrition	2.11

Note: Sort by Z-score value.

Visualisation Results of Keywords

Analysing keywords is very important for us to understand the research direction in this field. Since the heatmap produced by VOSviewer can more clearly display the popularity of keywords, we use VOSviewer to visualise keywords and draw keywords heatmap (Figure 6A). Keywords related to the topic, such as "ergothionein", "disease", "health", "nutrition" and keywords with less than ten occurrences, and merged synonyms (Type of analysis: Co-occurrence; Unit



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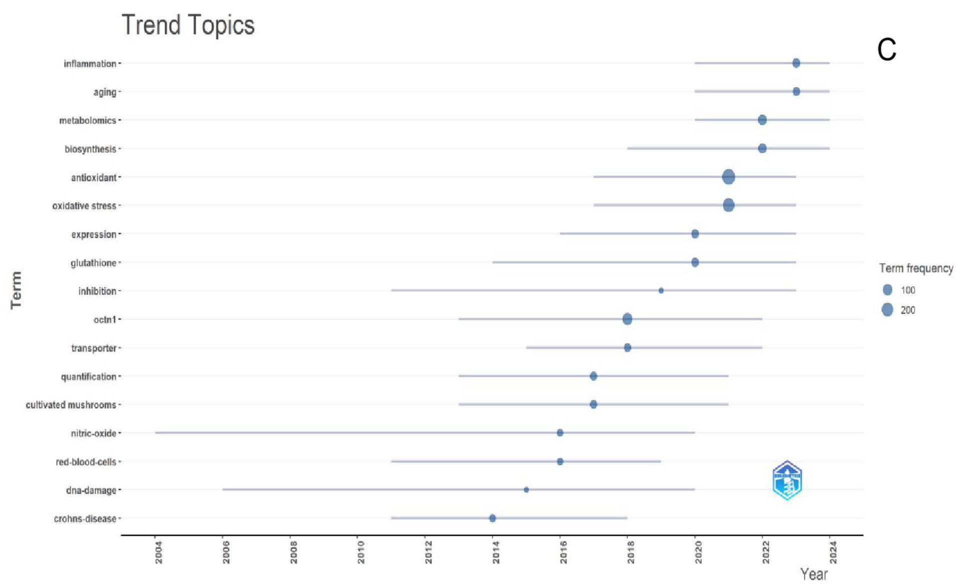

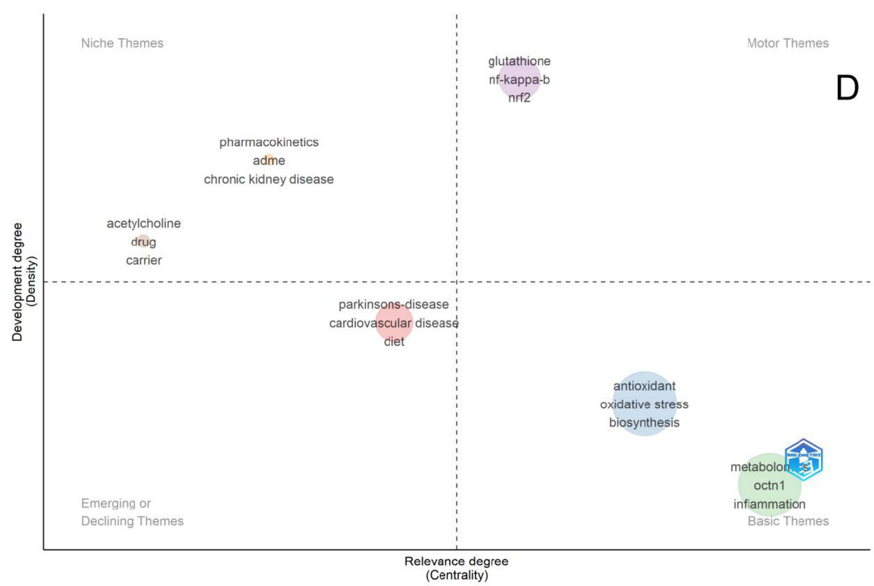

Figure 6 Keywords visualization. (**A**) Keywords heatmap. Heatmap uses different color shades to indicate the frequency of keywords; warm red represents hot zones, while cool blue indicates cold zones. (**B**) Cluster analysis of keywords by VOSviewer. Cluster 1: Red section; Cluster 2: Green section; Cluster 3: Blue section. (**C**) Trend Topics. (**D**) Telematic Map. The telematic map takes density as the vertical axis and centrality as the horizontal axis. The higher the density value, the higher the maturity of the topic, and centrality represents the connection between the topic and other topics. The closer it is to the right, the closer the connection between the topic and other topics.

analysis: All keywords) are excluded. The warmer the colour in the keyword heatmap, the higher the keyword occurrence frequency. Finally, we found 117 keywords that match the criteria, among which the most popular keywords are antioxidant (257), oxidative stress (191), OCTN1 (89), metabolomics (80), mushroom (70), biosynthesis (63), acid (59), in-vitro (53), identification (53), and inflammation (51).

Based on keyword visualization analysis, we used VOSviewer to cluster the keywords (Resolution: 0.8, Min. cluster size:1). The clustering results show that the keywords of EGT in biology and medical research can be divided into three categories (Figure 6B). Representing the three most popular research directions in this field, the four most popular keywords in each field are oxidative stress, metabolomics, identification, inflammation, (cluster 1, 55 keywords); antioxidant, mushroom, acid, in-vitro (cluster 2, 41 keywords); OCTN1, biosynthesis, glutathione, amino-acid (cluster 3, 21 keywords) (Figure 6B).

To better explain the evolution of the topic and discover emerging research trends, we used the Bibliometrix program package to create a "Trend Topics" chart for keywords (Figure 6C). The keywords that have exploded in recent years (after 2019) are inhibition, glutathione, expression, oxidative stress, antioxidant, biosynthesis, metabolomics, aging and inflammation (Figure 6C). The thematic evolution analysis diagram of keywords can be found in Figure S3. To understand the mechanism of action of EGT, we selected 245 articles related to the mechanism and target from 800 studies, and conducted telematic analysis on the keywords of these articles. The telematic map takes density as the vertical axis and centrality as the horizontal axis. The higher the density value, the higher the maturity of the topic, and centrality represents the connection between the topic and other topics. The closer it is to the right, the closer the connection between the topic and other topics. The results showed that the keywords in the upper right quadrant were "glutathione", "nf kappa b", and "nrf2", which were considered as motor themes. The keywords in the upper left quadrant "phamacokinetics", "adme", "chronic kidney disease", "acetylcholine", "drug", and "carrier" were identified as niche themes. "parkinsons-disease", "cardiovascular disease" and "diet" are identified as emerging or declining themes in the lower left quadrant. "antioxidant", "oxidative stress", "biosynthesis", "metabolomics", "octn1" and "inflammation" are identified as basic themes in the lower right quadrant (Figure 6D).

Discussion

Research Centres and Distribution of EGT in Biology and Medical Research Worldwide

The studies on EGT in biology and medical research have shown a trend of increasing publication and citation volume year by year, especially in recent years, with an average growth rate of 17.33% from 1996 to 2025. This is closely related to the increasingly mature production process and gradually decreasing production costs, in addition to EGT's strong antioxidant properties and enormous therapeutic potential. Based on the above data, we believe that EGT in biology and medical research will become a hotspot in the coming years. From the statistical results of countries/regions, the research hotspots in this field are mainly concentrated in the Americas, Asia, and Europe. China (215) and the USA (190) are undoubtedly the countries/regions with the largest research volume. The countries/regions with the closest cooperation are the USA (centrality: 0.44) and England (centrality: 0.34). From the current results, close cooperation between different regions has many benefits, such as innovating better extraction techniques, obtaining more sample sizes from different dietary structures and ethnic groups, and seeking breakthrough technologies for disease treatment. Therefore, we believe that strengthening regional connections is very important in the future. The analysis of institutional results shows that the National University of Singapore (28) ranks first in terms of publication volume, followed by Kanazawa University (26) in Japan, while Harvard University in the United States (18) has the highest centrality (0.33).

The analysis of high-impact authors shows that among the top ten authors in terms of publication volume, six are from Asia, three are from Poland in Europe, and one is from the USA in the Americas. Those authors are basically from those top 10 institutions as mentioned previously. Among them, Halliwell B (169) has the highest H-index ranking. Regardless of the number of publications or H-index, Halliwell B is undoubtedly an authority on EGT in the medical field. Halliwell B mainly researches the antioxidant and anti-aging effects of EGT.[11,30,65,66] From the centrality results, the majority of authors have a centrality of 0.00, indicating that there is no close collaboration among authors in this field. It is hoped that there will be closer collaboration among authors in the future.

Research Hotspots and Frontiers

Among the top five cited articles, three of which mainly study the antioxidant properties and mechanisms of EGT, and one article focuses on the transport protein channels of EGT.[4,31,67,68] From the perspective of highly cited literature, the most concerning aspect of EGT is its antioxidant capacity. In addition, Chen Y mentioned the causal relationship between EGT and asthma and inflammatory bowel disease in his article published in *NATURE GENETICS*, which further highlights the importance of EGT in disease treatment and diagnosis.[69]

According to the visualisation analysis of keywords, the most popular keywords are antioxidant (257), oxidative stress (191), OCTN1 (89), metabolomics (80), mushroom (70), biosynthesis (63), acid (59), in-vitro (53), identification

(53), inflammation (51). The results of the "Trend Topics" chart show that the keywords that have exploded in recent years (after 2019) are inhibition, glutathione, expression, oxidative stress, antioxidant, biosynthesis, metabolomics, aging and inflammation. The clustering analysis of VOSviewer shows that the four most popular keywords in each field are oxidative stress, metabolomics, identification, inflammation, (cluster 1, 55 keywords); antioxidant, mushroom, acid, in-vitro (cluster 2, 41 keywords); OCTN1, biosynthesis, glutathione, amino-acid (cluster 3, 21 keywords). The keyword statistics of VOSviewer show that keywords can be roughly divided into three groups. Based on the above results, we analyze the themes of this field from three directions to speculate on its hotspots and future research directions.

The Absorption, Distribution, Anti-Inflammatory and Antioxidant Biological Molecular Mechanisms of EGT in vivo

EGT has been proven to be unable to synthesise on its own in the human body and can only be obtained through food. OCTN1 is a highly specific transporter of EGT, and EGT in food can be effectively absorbed by OCTN1 in the intestine and rapidly distributed to cells and tissues in contact with the blood. The level of EGT is highest in the liver and red blood cells, and also higher in the spleen, kidneys, lungs, heart, intestines, eyes, and brain tissues.[70] It is interesting that EGT accumulates in tissues and organs that experience oxidative stress and inflammation, so supplementing EGT can reduce inflammatory markers.[33,51] For example, a human study by Cheah et al[9] showed that after administering EGT, there was a slight decrease in oxidative damage and inflammatory biomarkers. In addition, recent research results have shown that serum EGT levels are related to dietary structure.[71] A cross-sectional study conducted by Suzuki et al[72] on Japanese residents in recent years showed a positive correlation between serum EGT concentration and foods such as fish (r=0.215, p<0.001), mushrooms (r=0.202, p<0.001), and grilled fish (r=0.200, p<0.001).

EGT has strong antioxidant capacity. From keyword visualisation analysis and keyword citation explosion, it can be seen that antioxidant has always been a focus of EGT research in biology and medical research. According to current research, the antioxidant effect of EGT is mainly achieved through the following three mechanisms: 1) Free electron binding with hydroxyl radicals (· OH), peroxynitrite (ONOO -), nitroso peroxycarbonate (ONOOCO -), and hypochlorite (ClO -) EGT is a tautomeric structure with two forms: thione and thiol. EGT mainly exists in the form of thione and has a high oxidation-reduction potential. Therefore, EGT can eliminate free radicals through its high redox potential.[10,73,74] 2) EGT can interact with other natural antioxidant defense systems to enhance the body's antioxidant capacity.[75–77] Research has shown that EGT can significantly increase glutathione levels and accelerate the circulation of glutathione and oxidized glutathione (GSSG).[78] Tsay et al[79] found that the pairwise combination of EGT, Ferulic Acid (FA), and Glutathione (GHS) can increase antioxidant capacity. When 50 μM EGT is combined with 100 μM FA, EGT exhibits stronger antioxidant properties. The study by Li et al[80] showed that EGT could upregulate Phosphatidylinositol-3-kinase (PI3K) Signals and Increase Nuclear factor erythroid 2-related factor 2 (Nrf2) Level to exert antioxidant effects. Recent experimental results such as Meng et al[81] have shown that EGT can reduced reactive oxygen species (ROS) levels by regulating the DJ-1-Nrf2 pathway. 3) EGT can chelate various divalent metal cations, such as iron, copper, zinc, nickel, and cobalt, to exert antioxidant capacity[82] (Figure S4). In recent years, many scholars have constructed cells or models for various diseases, such as Parkinson's disease, metabolic dysfunction related to fatty liver disease, rheumatoid arthritis, aging cells, etc. Their results have shown that EGT can protect cells by clearing and reducing oxygen species (ROS).[83–86] From current research, the antioxidant capacity and mechanism of EGT on aging cells and inflammatory damaged cells will still be an important research direction in the future.

In previous studies, EGT has been found to have anti-inflammatory properties.[9] It is known that there are several inflammatory factors involved in the inflammatory response, including TNF-α, interleukin-1β (IL-1β), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β). The current results show that EGT can regulate various inflammatory factors such as TNF - α, IL-1 β, IL-6 by modulating the NF-κB, mitogen-activated protein kinase (MAPK), and Phosphatidylinositol-3-kinase/Protein kinase B (PI3K/AKT) signaling pathways.[87] Salama et al[88] administered 70 mg/kg EGT to rats daily for 10 consecutive days, and set up a pure iron group (injected with 30 mg/kg iron glucan saline) and an iron^{+} EGT group. The results showed that EGT combined administration could reduce iron induced nuclear translocation of NF-κB p65 by 43%, and reduce TNF-α and IL-6 levels by 46% and 55%, respectively (with significant differences compared to the pure iron group, $p<0.05$). The experiment by Koh et al[89] showed that EGT significantly reduced the mRNA expression of pro-inflammatory cytokines IL-1 β, IL-6, IL-8, TNF-α, and cyclooxygenase-2 in brain endothelial cells induced by 7-ketocholesterol (7kc) ($p<0.01$). In addition, recent studies have shown that EGT can improve placental inflammation induced by NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and caused by the increase of mitochondrial superoxide produced by macrophage subsets in pregnant diabetes patients.[90]

The results of the telematic analysis of EGT mechanism research show that "glutathione", "nf kappa b", and "nrf2" are motor themes, indicating that these themes have developed well and are very important. The words "phamacokinetics", "adme", "chronic kidney disease", "acetylcholine", "drug", and "carrier" were identified as niche themes. These themes are not important in this field and have already developed well. The words "parkinson's disease", "cardiovascular disease" and "diet" located in the lower left quadrant indicate that these are new or soon to disappear themes. It is worth noting that although these words are located in the lower left quadrant, they are relatively close to the center and still have some potential for future development. The keywords located in the lower right quadrant are "antioxidant", "oxidative stress", "biosynthesis", "metabolomics", "octn1" and "inflammation" indicating that these topics are low maturity foundational topics that may become research hotspots in the future (Figure 6D).

The Impact of EGT's Antioxidant and Anti-Inflammatory Effects on Various Diseases

From the currently known research results, the most concerned ability of EGT is its antioxidant and anti-inflammatory properties. Based on these two characteristics of EGT, studies have found that it is associated with the treatment and occurrence of various disease states, such as neurodegenerative diseases (ARND), aging, inflammatory bowel disease, etc.[34,67,91,92]

From the results of keyword visualization analysis, it can be seen that the role of EGT has received early attention and has developed rapidly in the fields of ARND and aging research. At present, EGT has achieved certain basic theoretical results and clinical trial results in this field. EGT is considered to have strong antioxidant capacity, and oxidative stress is an important factor in causing ARND.[93–96] Therefore, the use of EGT to treat ARND is considered to have great research prospects. But currently, the research on the effects of EGT on nerve cells is mainly focused on animal models and in vitro studies. According to the systematic review by Takhor et al[97] there were a total of 19 studies on ergothionein in ARND from 2015 to October 5, 2024, including 7 studies with humans as samples and only 1 RCT study (Yau YF's pilot study was not included in the following text due to publication later than the statistical time[17]). In animal experiments, the research subjects are generally animal models or in vitro studies using animal cells. In recent years, in vitro studies by Apparoo et al[98] have shown that the use of mushroom ethanol extract rich in EGT significantly increased cell viability and reversed neuronal aging induced by oxidative stress in aging mouse hippocampal neurons after 8 hours of incubation. The impaired clearance of β - amyloid protein (Aβ) is an important cause of Alzheimer's disease. Wijesinghe et al[99] found that in a mouse model of Alzheimer's disease treated with EGT, the average count of Aβ deposition in the treatment group (3.74 ± 0.37) was significantly lower than that in the untreated group (5.83 ± 0.75) ($p=0.036$) compared to the control group. In the study of EGT treatment for ARND, there are few experiments that use humans as research subjects. The main types of research are cohort study, case control study, cross-sectional study, and randomized controlled trial (RCT). Cohort study, case control study, and cross-sectional study often analyze the relationship between EGT and ARND by measuring the level of plasma EGT[100] For example, a cohort study by Oka et al[101] showed that for patients with mild cognitive impairment (MCI), lower EGT levels in the blood are more likely to develop AD earlier, with a 12% higher rate of AD progression within two years compared to patients with high EGT levels in the blood. There are few RCT experiments in the EGT treatment of ARND, and the sample sizes are not large. In a randomized controlled trial conducted by Ishimoto et al[18] 48 MCI patients were recruited and orally administered 5mg EGT or placebo tablets once a day for 12 weeks. The results showed that the Phosphorylated Tyrosine Kinase Receptor B (p-TrkB/TrkB) ratio in the serum Extracellular Vesicles (EVs) of the treatment group was significantly higher at week 8 and week 12 than week 0 ($p<0.05$), and the serum ergotamine concentration was significantly correlated with the p-TrkB/TrkB ratio ($p<0.05$, correlation coefficient $r=0.177$). Ishimoto et al[18] used Cognitrax to evaluate cognitive function, and the results showed that the cognitive function of the treatment group was significantly positively correlated with the p-TrkB/TrkB ratio and the Δ AUC of serum EGT (indicating an increase in systemic exposure to EGT after oral administration of EGT containing tablets), composite memory (p-TrkB/TrkB: $p<0.01$, $r=0.286$; ΔAUC for Serum ERGO: $p<0.05$, $r=0.244$), verbal memory (p-TrkB/TrkB: $p<0.05$, $r=0.215$; ΔAUC for Serum ERGO: $p<0.05$, $r=0.240$) and processing speed (p-TrkB/TrkB: p<0.05, $r=0.204$; ΔAUC for Serum ERGO: $p<0.05$, $r=0.204$). The amount of research related to randomized controlled trials (RCTs) is relatively small, but has gradually increased in recent years. Yau et al[17] recently conducted a randomized double-blind pilot study in which 19 mild cognitive impairment patients aged 60 and above received EGT (25mg per pill) or placebo, three times a week for one year. The results also showed that compared with the placebo group, subjects receiving EGT treatment showed significant improvement in learning ability assessment. However, this experiment is only a pilot study, so the final conclusion still needs to wait for the results of subsequent research. In research on aging, in recent years, an increasing number of studies have shown that EGT has protective and preventive effects on some age-related diseases. The shortening of telomeres caused by oxidative stress is associated with various age-related diseases. Research has shown that EGT can reduce the telomere shortening rate and maintain telomere length under oxidative stress conditions.[102] The study by Katsube et al[103] found that mice receiving 4–5 mg/kg/day of EGT supplementation from 7 weeks of age had significantly prolonged survival time ($p<0.001$). For mice taking EGT, the median and average survival ages increased by 16% and 21%. From the above studies, it can be seen that the targets and mechanisms of EGT therapy for ARND and aging are still hot research topics. And currently, scholars have also begun to attempt clinical trials, even randomized controlled double-blind trials. However, the current clinical trial data is still limited. Therefore, we believe that in future research, the treatment of ARND and aging with EGT will require more support from clinical trial data.

Besides, inflammatory bowel disease-related keywords have also frequently appeared in recent years of studies. Currently, research on Crohn's disease still remains at the level of biological molecular mechanisms and animal experiments, lacking relevant clinical trial studies. Peltekova et al[104] discovered that functional variations in the organic cation transporter protein (OCTN) of EGT were associated with Crohn's disease. Kato et al[34] found that in a mouse model with OCTN1 gene knockout, octn1 (-/-) mice exhibited greater susceptibility to intestinal inflammation under ischemia-reperfusion conditions. Therefore, the expression of OCTN1 and serum concentration of EGT are also considered to be possible for identifying susceptibility to inflammatory bowel disease.[105,106] Recent studies have shown that EGT also has a protective effect on ulcerative colitis. Pang et al[107] found that 40 mg/kg EGT gavage can regulate dextran sulfate sodium-induced ulcerative colitis in rats. The expression of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α in the experimental group decreased ($p<0.05$). At the same time, the research results showed that EGT could inhibit toll-like receptor 4/myeloid differentiation factor 88/nuclear factor κB (TLR4/MyD88/NF-κB) Signal pathway ($p<0.05$) significantly inhibits colonic shortening and alleviates colonic pathological damage Oxidative stress and inflammation are the characteristics of atherosclerosis. Smith conducted a 21.4 year study on 3236 participants and found that EGT was associated with a lower risk of coronary heart disease.[108] Martin's[109] experiment showed that under inflammatory conditions, mushrooms can inhibit the activity associated with cardiovascular disease cellular processes such as adhesion molecule expression and binding of monocytes to the endothelium.

From the visualization analysis of keywords, it can be seen that EGT has been extensively studied and theoretically matured in the treatment of neurological diseases, especially in the treatment of cell aging and DNA damage. Therefore, we believe that the next research direction will be to elucidate therapeutic targets and increase clinical data. However, for other inflammation related diseases such as inflammatory bowel disease, cardiovascular disease, the current conclusion is that consuming mushrooms may be beneficial, but there is a lack of human clinical trials on whether supplementing EGT can treat related diseases. The therapeutic relevance of EGT for these diseases requires further in vitro studies, animal models, and other data to better elucidate its mechanisms and provide more theoretical basis for future clinical research.

The Source of EGT, the Antioxidant Potential of Edible Fungi in vitro, and Its Influencing Factors

The preparation methods of EGT mainly include natural product extraction, chemical synthesis, and biosynthesis. EGT was first isolated from the fungus *Claviceps purpurea (C. purpurea)* by Tanret C in 1909, which was also the source of early EGT. However, *C. purpurea* itself contains toxic substances such as ergot alkaloids (such as ergotamine and ergometrine)

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and lysergic acid diethylamide (LSD) precursors that have vasoconstrictive and hallucinogenic functions. In order to reduce the occurrence of toxic substances during extraction, current processes tend to extract EGT from edible mushrooms such as *Lentinula edodes*, which not only have high EGT content but are also relatively safe.[110,111] That's precisely why many scholars believe that edible fungi will become the next healthy food.[42,112] Natural product extraction methods generally include reflux extraction, enzymatic extraction, and ultrasound microwave combined method. The research on the influence of EGT extraction concentration focuses on the types of edible fungi,[113] the cultivation process of edible fungi,[114,115] and the extraction process.[116,117] The study by Apparoo[98] compared 14 types of mushrooms and found that the highest EGT content was found in *Lentinula edodes*. Kim[115] found that using blue light during mushroom cultivation can increase the EGT concentration of mushrooms, thereby enhancing their antioxidant capacity ($p<0.05$). Huang[118] focused on *Cordyceps militaris* and found that after ultraviolet-B (UV-B) light irradiation, the amount of EGT of fruiting bodies dramatically increased. A recent study by Zhang[117] evaluated the effect of different drying processes on the antioxidant capacity of *Pleurotus citrinopiletus Singer (P. citrinopiletus)*. The final results indicate that natural ventilation and drying can increase the EGT content in mushrooms. When the pressure is 250MPa, the solvent is distilled water, the liquid-solid ratio is 1:10, and the extraction time is 52min, the highest EGT content is extracted, which is 4.03mg/g ± 0.01mg/g.

The traditional chemical synthesis method of EGT mainly uses *L*-histidine as the starting material, and synthesizes EGT in aqueous solution through multi-step reactions such as thiolation, thiol protection, methylation, and deprotection.[119] However, the traditional chemical synthesis method has low efficiency and high cost. In recent years, the chemical synthesis of EGT has been improved by mimicking the biosynthetic pathway. Erdelmeier et al[120] used hercynine (HER) as the raw material, and combined it with L-cysteine (*L*-Cys) and 3-mercaptopropionic acid (3-MPA) in a "one pot method" to produce EGT, with a total yield of 40.00%. Obviously, although biological extraction and chemical synthesis methods have been improved, there are still limitations such as high cost and low safety. Simultaneously, chemical synthesis often cannot avoid the residue of harmful substances. Therefore, the mainstream technology has shifted towards biosynthesis of EGT.

The synthesis pathway of EGT in many microorganisms has been elucidated. For example, Seebeck[121] elucidated the aerobic biosynthesis pathway of EGT in *Mycobacterium smegmatis*. He finds that *EgtA, EgtB, EgtC, EgtD*, and *EgtE* are genes related to the aerobic synthesis pathway of EGT. It is worth noting that in the fungal biosynthetic pathway, EGT only involves two synthase genes *Egt1* and *Egt2*.[122] Therefore, the synthetic pathway of fungi is simpler than that of bacteria. The above synthesis pathways are all aerobic synthesis pathways, and EGT can also be synthesized through anaerobic pathways, but it depends on an anaerobic bacterium called *Chlorobium limicola*.[123] However, compared to aerobic pathways, the anaerobic synthesis pathway of EGT is more complex and therefore has not been widely applied. Although various microorganisms have been reported to have the ability to synthesize EGT, the self-production of wild-type strains is far from meeting the needs of industrial production. Therefore, researchers have constructed a series of engineered strains based on the biosynthesis pathway of EGT. Engineering bacteria refer to modified strains of bacteria that efficiently express specific products by introducing exogenous target genes into microbial cells through genetic engineering technology. Compared to other methods, the preparation of EGT using engineered bacteria has advantages such as low cost, high yield, safety, and environmental friendliness. For example, Kamide discovered that *Methylobacterium* strains contains a special EgtBs enzyme similar to Egt1 in fungi. Kamide cloned the gene encoding this EgtBs enzyme into Escherichia coli and fermented it for 216 hours, resulting in an EGT yield of 657 mg/L.[124]

Based on the above results, we believe that the biosynthesis of EGT will be a research hotspot in the future, with further optimization of engineered strains and purification of EGT being the next research directions.

Strengths and Limitations

To our understanding, this study has conducted a bibliometric analysis for the first time on the research trends of EGT within the realm of biology and medical sciences, thereby identifying, to a certain extent, the emerging research trends, hotspots, and frontiers in this domain. However, it is worth noting that our research does possess certain limitations. Firstly, our articles are all from the WOSCC and SciFinder database, which may lead to overlooking other high-quality literature. Secondly, it cannot be ruled out that some literature was not retrieved due to limitations in the search, resulting in bias. Thirdly, although we have conducted visual analysis and clustering of keywords using software, the classification of research directions and the summary of specific research directions of highly influential authors in this field still rely heavily on the subjective analysis and classification of the authors, lacking classification basis, and the results may not be objective enough. Finally, our study has inherent lag, and some new studies may not be included.

Conclusion

EGT's research centers are currently mainly located in Asia, America, and Europe, and Halliwell B from the National University of Singapore is an authority in this field. Currently, multiple countries have issued usage licenses for EGT. The demand for EGT's super antioxidant capacity in the fields of health products, cosmetics, and medical care, policy approvals and increasingly sophisticated preparation processes have all rapidly driven the research and development of EGT. Therefore, we predict that EGT will become the next trend. For mechanism research, the themes corresponding to keywords such as "glutathione", "nf kappa b" and "nrf2" are very important and have developed well. However, the targets and mechanism of EGT are not yet clear. This is also an important reason that constrains the development of EGT. In the research for diseases treatment, EGT has received early attention in the field of ARND and aging. At present, it has a certain theoretical basis, but the basic research on the treatment of Crohn's disease, diabetes and other inflammatory related diseases is still insufficient. For EGT preparation, biosynthesis is currently the mainstream due to its safety and high yield characteristics.

In the future, we believe that the following will be research hotspots: 1) In terms of mechanism research, the keywords "antioxidant", "oxidative stress", "biosynthesis", "metabolomics", "octn1" and "inflammation" represent mature and low basic themes, which are future research directions. 2) EGT treatment for ARND, aging and other related diseases requires more clinical data, while inflammation related diseases require more basic research. 3) Further screening of microorganisms that can achieve high yields. Developing more economical and safer engineering bacteria to further promote the development of EGT.

Data Sharing Statement

Publicly available datasets were analysed in this study. These data can be found at: https://webofscience.clarivate.cn/wos/woscc/basic-search, https://scifinder.cas.org.

Ethical Approval and Consent to Participate

This study did not involve human or animal subjects. The literature used was sourced from the publicly available databases "Web of Science" and "SciFinder", therefore ethical approval is not required. The research plan followed the guidelines established by the journal.

Consent for Publication

This study has not been publicly published before, nor has it been considered for publication elsewhere. This publication has been approved by all co-authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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