Original Article

Emerging trends and hotspots in chronic obstructive pulmonary disease and oxidative stress: a bibliometric and visualized analysis from 2010 to 2024

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Background: Chronic obstructive pulmonary disease (COPD) is a long-term respiratory condition defined by ongoing respiratory symptoms and restricted airflow, resulting in high rates of morbidity, mortality, and disability for this condition. Due to the incomplete understanding of its pathogenesis, no permanent curative measures or specific drugs are available. In recent years, a multitude of research has highlighted the substantial influence of oxidative stress on the development of COPD; however, there has been a deficiency in bibliometric analyses focusing on research trends and hotspots in the field. Therefore, our study aimed at presenting the emerging trends and hotspots related to COPD and oxidative stress.

Methods: Publications concerning oxidative stress in COPD were obtained from the Web of Science Core Collection database, covering the period from 2010 to 2024. On July 25, 2024, all relevant data were downloaded, followed by a process of data screening and analysis.

Results: The analysis incorporated 1,308 articles and 440 reviews, involving contributions from 1,034 researchers affiliated with 512 institutions across 64 countries published in a total of 548 journals. Through a series of analyses using five visualization tools, we identified the top 5 most productive countries, institutions, journals, and highly co-cited journals in the field from 2010 to 2024. We also identified 12 citation clusters, 10 influential authors, co-cited authors and articles, and 11 keyword clusters, established the top 20 keywords, and observed the evolution of reference and keyword bursts.

Conclusions: This study is the first to quantitatively capture the progress of oxidative stress in the field of COPD research, and the results show a marked upward trend in recent years in terms of research on COPD and oxidative stress. Developing novel effective antioxidants is becoming the future direction for COPD treatment. Besides antioxidant therapy, exposure (to air pollution), cigarette smoke, and mitochondrial dysfunction emerged as prominent research hotspots. This extensive bibliometric study offers significant insights into the exploration of oxidative stress in publications related to COPD with the purpose to support and enhance future scientific research for investigators in the field.

Keywords: Oxidative stress; chronic obstructive pulmonary disease (COPD); bibliometric analysis; CiteSpace; VOSviewer

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Introduction

Chronic obstructive pulmonary disease (COPD) is a globally prevalent chronic lung disease that frequently causes disability, impacting over 250 million individuals worldwide. Based on research findings, this disease accounted for 3.2 million fatalities in 2017, positioning it as the third most significant contributor to global mortality. Forecasts suggest that COPD will be responsible for approximately 4.4 million annual deaths by 2040 (1). Although the precise mechanism that contributes to the development of COPD remains unclear, emerging research indicates that oxidative stress could be a crucial factor in its pathogenesis (2).

The concept of oxidative stress was initially proposed in the biological literature in 1970 (3). It was later expanded upon in the publication "Oxidative Stress: Concepts in Reduction and Oxidation (REDOX) Biology and Medicine", which defines it as an imbalance favoring oxidants over antioxidants (4). This imbalance is capable of disrupting REDOX signaling and regulation, resulting in molecular damage (5). Recognized as a pathogenic mechanism of COPD, oxidative stress can activate inflammatory genes, promote mucus hypersecretion, and deactivate antiproteases, leading to various detrimental effects on lung tissue (6).

Bibliometry is a quantitative technique employed to characterize and analyze the development and advancement of a particular area and research domain. Leveraging modern computer technology, the author's organizational documents are scrutinized, and the analysis outcomes are visually represented through knowledge graphs. Scholars specializing in bibliometrics have emphasized that visual analysis enhances data interpretation, ensuring comprehensive results while facilitating the exploration of internal information connections, thereby aiding our comprehension of a particular field's research status and trends (7).

Highlight box

Key findings

- Oxidative stress is a prominent area in chronic obstructive pulmonary disease (COPD) studies. "Exposure (to air pollution)", "cigarette smoke extract", "mitochondrial dysfunction", and "antioxidant" are becoming hot topics.

What is known and what is new?

- Although oxidative stress has a substantial impact on the progression of COPD, there has been a deficiency in bibliometric analyses focusing on research trends and hotspots in the field.
- This study conducted a comprehensive and visual analysis in the field of oxidative stress and COPD, providing new ideas for future scientific research.

What is the implication, and what should change now?

- The key role of oxidative stress in the occurrence and development of COPD has been confirmed, but the efficacy of antioxidants developed from oxidative stress in the treatment of COPD is limited. Follow-up research should be continuously strengthened to develop precisely targeted antioxidants that effectively act on specific cellular compartments.

Methods

Data source

To obtain authoritative data for this study, we searched publications from the Web of Science Core Collection (WoSCC) database (8) and selected the SCI-EXPANDED database as the source of available databases. Due to the strict criteria and standards concerning data quality of the bibliometric analysis software, we chose the WoSCC database as our primary source for data acquisition. It should be noted that the WoSCC database has limited coverage of non-English literature, which may contribute to the comprehensiveness and diversity of this study being limited on a global scale.

Search strategy

The search formula was configured as "TS=("Reactive Oxygen Species" OR "Oxidative stress") AND TS = ("Pulmonary Disease, Chronic Obstructive" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Airflow Obstruction*Chronic" OR "Chronic Airflow

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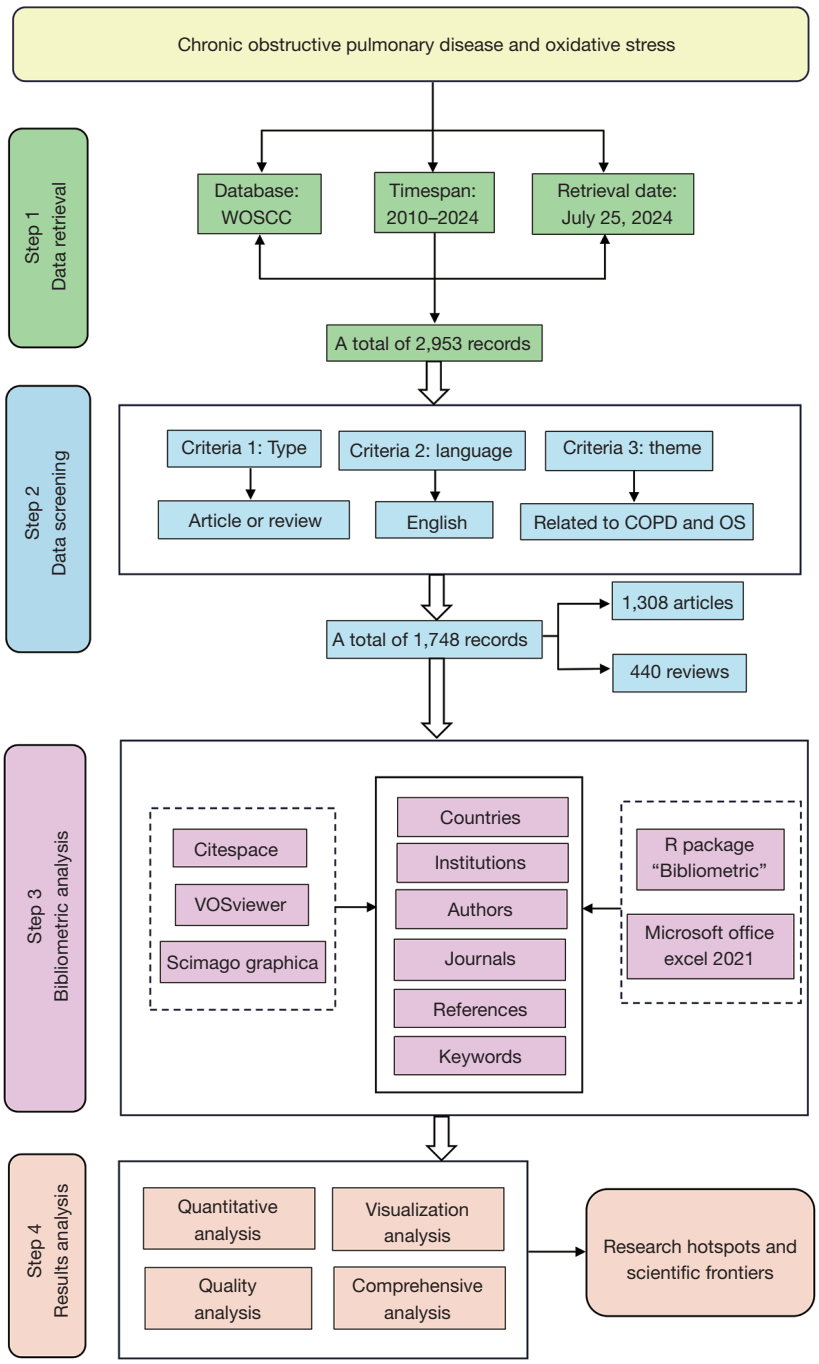

Figure 1 Flow chart of data screening and analysis process. WOSCC, Web of Science Core Collection database.

Obstruction*") AND Language = English" (9,10). We set a period of publication paper retrieval from January 1, 2010, to December 31, 2024, and restricted the publication types to "article" or "review", with a total of 2,936 records. To maintain data consistency, we downloaded all pertinent information and filtered out (*Figure 1*) irrelevant publications carefully by two researchers (S.F. and J.J.). After completing this procedure, we successfully acquired 1,748 related publications as our primary data. Then we exported target data regarding authors, journals, countries,

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institutions, keywords, and references of these publications in plain text files and tab-delimited files separately.

Data analysis

The scientific tools CiteSpace, VOSviewer, Scimago Graphica, R package "Bibliometric", and Microsoft Office Excel 2021 were employed for an analysis of the progress in understanding oxidative stress in COPD from 2010 to 2024, emerging trends, and hotspots.

We employed CiteSpace, a Java-based bibliometric tool, to visualize the relationships among documents in the form of a scientific knowledge map (11). It is able to conduct a fundamental analysis of author co-occurrence and collaboration, as well as analyze the co-occurrence patterns among journals, institutions, and countries. The clustering and mutation analysis of keywords and co-cited documents can also be carried out (12). In this research, we utilize CiteSpace co-occurrence analysis to examine the partnerships of authors or institutions, generating a network graph wherein each node represents either an author or institution. The size of each node is proportional to its significance within the network. Larger nodes show greater significance in their respective fields; meanwhile, connections between nodes signify co-occurrence or co-citation relationships with connection thickness reflecting cooperation density between two entities. Thicker connections denote closer collaboration ties. Additionally, cluster analysis is utilized for information classification to explore similar topics effectively (13). Outbreak analysis enables us to identify sudden surges in popularity regarding certain topics at given timeframes promptly, thus assisting us in swiftly identifying actively discussed hot topics. The combined application of CiteSpace co-occurrence analysis, clustering techniques, and outbreak analysis facilitates exploration into evolving research trends within specific disciplines or knowledge domains alongside understanding their relationship with cutting-edge hotspots as well as related knowledge bases—ultimately enabling discovery and examination of the latest research directions.

VOSviewer is an application for bibliometric mapping created by Van Eck and Waltman at Leiden University's Center for Scientific and Technological Research in 2010 (14), which offers three visualization techniques, including overlay visualization, network visualization, and destiny visualization. Besides, it can clearly show the co-occurrence and co-citation relationship between the authors, journals, references, or keywords through different representations.

Scimago Graphica (15) is a data visualization tool developed by Scimago Lab. The tool enables the visualization of journal rankings and impact, facilitates the analysis of scientific output across different disciplines and nations, and offers dynamic visualizations that can be customized based on selected time frames and metrics. Users can interact with the data by utilizing various functions, such as filtering and scaling, to tailor the analysis to their needs. In our study, Scimago Graphica is utilized to generate interactive charts and maps, illustrating the spatial dispersion of oxidative stress publications in COPD.

R package "Bibliometric" (16) is a novel open platform tool for mapping scientific literature, whose results are presented in intuitive images or tables for effective data visualization. This tool primarily serves to acquire and analyze literature data from a variety of databases. It extracts relevant information and performs calculations for bibliometric indicators, such as impact factor, H-index, G-index, and citation counts. By offering a comprehensive analysis of academic data from multiple perspectives, the package helps uncover relationships within the literature. Additionally, it provides valuable statistical insights that enhance the efficiency and clarity of the analysis process. Simultaneously, Microsoft Office Excel 2021 is employed to perform quantitative analysis of the data.

Results

Number of publications and citation trends

Our study analyzed 1,748 publications on oxidative stress in COPD, including 1,308 articles and 440 reviews (*Figure 1*), authored by 1,034 researchers from 512 institutions in 64 countries, and published in 118 journals.

Based on the data presented in *Figure 2*, the line chart shows a noticeable increase in annual publication volume within this field starting from 2019. Moreover, it is worth mentioning that the publication rate has consistently remained at a high level, especially since the number of publications has remained stable at more than 150 articles per year since 2021. Furthermore, the polynomial curve shows a positive correlation between the year and the number of annual publications (R^2=0.9074) (17). These results suggest that there has been a growing focus on oxidative stress in the past few years, making it a prominent area of interest in COPD studies.

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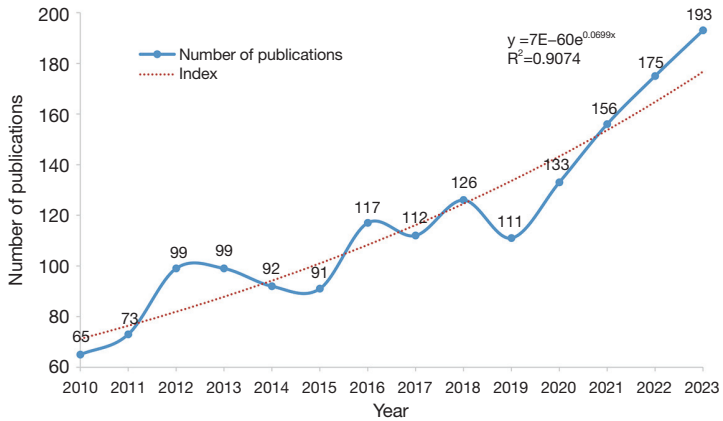

Figure 2 The annual quantities and growth trends of publications from 2010 to 2023.

Analysis of countries and institutions

The statistical results show that 512 institutions across 64 countries actively participated in the research on COPD and oxidative stress. *Figure 3A* visually illustrates the dispersion and inclusion of these nations, whereas *Tables 1,2* display the quantity of articles published by the leading 10 countries and institutions. China secured the first position with 490 publications, while the USA followed closely behind with 325, and the UK ranked third with 149. Notably, in terms of average citation count, the UK ranked first with 73.84, highlighting its exceptional recognition and contribution in this field.

Regarding international collaboration in the domain, several nations have forged strong partnerships. As illustrated in *Figure 3B*, the findings indicate a direct correlation between a country's publication output and its level of collaboration. China, which published the most articles, has formed tight cooperation with the USA, Italy, and the UK. In addition, the USA, Britain, Italy, and Germany have also established extensive cooperation with other countries.

Figure 3C illustrates the publication counts and collaborative connections among various institutions. Imperial College London stands out as the leading contributor in this domain. Notably, the two authors with the highest publication counts in this field are also affiliated with Imperial College London. The majority of the top 10 institutions are located in China, the USA, the UK, and Australia in general.

Analysis of leading journals and co-cited journals

In this study, a total of 548 journals have published articles on the topic of COPD and oxidative stress. Firstly, to identify high-impact journals in this field, we visualized those journals with eight or more articles using VOSviewer as shown in *Figure 4*. *Table 3* provides a list of the top 10 journals in this study. The *International Journal of Chronic Obstructive Pulmonary Disease* has emerged as the leading journal in this field, publishing a total of 69 articles. It is followed by *Respiratory Research*, which has contributed 51 articles, while the *International Journal of Molecular Sciences* ranks third with 38 articles. Notably, *The American Journal of Respiratory and Critical Care Medicine* ranks among the top 10 journals with 25 articles and is distinguished as the most co-cited journal, boasting a remarkable citation count of 1,381 and an impact factor of 19.3 for 2024, highlighting its substantial influence within the scientific community. *Table 4* provides specific data on these metrics along with a list of the top 10 co-cited journals. A total of 7,539 co-cited journals were used in the analysis results. The *European Respiratory Journal* follows closely behind *The American Journal of Respiratory and Critical Care Medicine* in second place with a citation count of 1,277, while *Chest* secures third place at 1,042 citations. To obtain a better visualization, we present only well-known journals that garnered over 300 co-citations in *Figure 4*. Additionally worth mentioning is the *Lancet* which holds the ninth position among co-cited journals receiving a notable citation count of 759 and boasts an impressive impact factor of 98.4 in 2024, signifying its strong influence in the scientific community.

Analysis of the lead authors and co-cited authors

Analyzing the authorship of the literature allows us to identify key scholars and primary research contributors in the field. From 2010 to 2024, a total of 1,034 researchers

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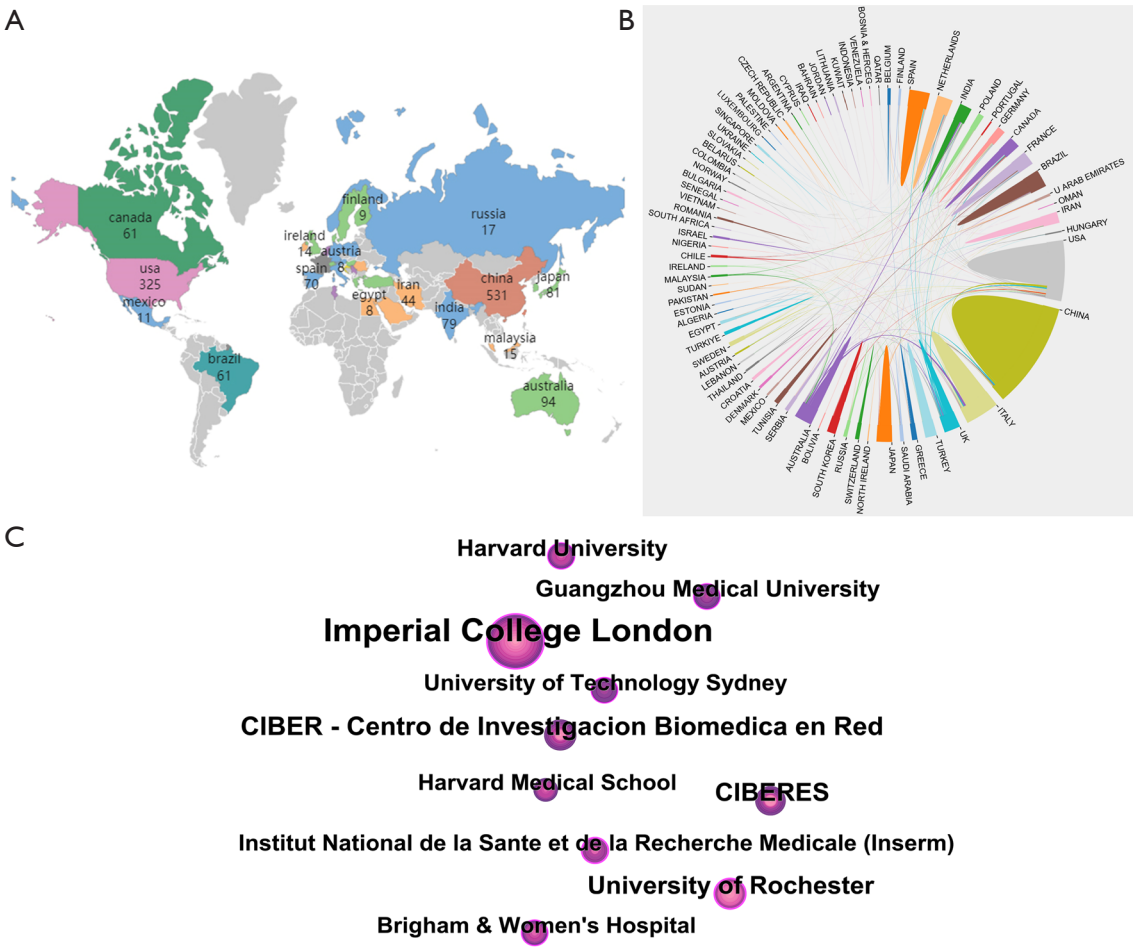

Figure 3 Visual map of countries and institutions in related domain. (A) Map regarding the geographical spread of publications among different countries. (B) A map representing collaborative publication efforts between nations. (C) A visual node diagram of institutions.

Table 1 Top 10 active countries

Rank	Country	Records	Citations
1	China	490	8,735
2	USA	325	16,059
3	UK	149	10,928
4	Italy	148	7,227
5	Australia	94	3,168
6	Japan	81	2,769
7	India	79	2,176
8	Netherlands	70	3,023
9	Canada	61	2,460
10	France	58	1,903

engaged in studies focused on oxidative stress in COPD. The top 10 authors, ranked by the number of published papers related to this topic, are presented in *Table 5*. Barnes, Peter J. from Imperial College London, ranking first with 47 articles. He has profound research on the major contributors and pathogenesis of respiratory diseases, especially the main coping pathways, related coping strategies, and new targets for COPD therapy (18-22). In order to learn about the high-contributing scholars in the field, we only visualized the prolific authors in the field with more than 10 publications using VOSviewer shown in *Figure 5A*. As the size of the circular nodes increases, it reflects a greater number of publications, while thicker connecting lines indicate a stronger association. This suggests that more frequent collaborations among authors

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Table 2 Top 10 active institutions

Rank	Institutions	Records	Citations
1	Imperial College London	91	5,496
2	CIBER - Centro de Investigacion Biomedica en Red	33	2,764
3	CIBERES	29	1,766
4	University of Rochester	28	2,583
5	Guangzhou Medical University	21	687
6	Harvard University	21	1,021
7	University of Technology Sydney	20	605
8	Institut National de la Sante et de la Recherche Medicale	20	1,188
9	Harvard Medical School	19	930
10	Brigham & Women's Hospital	19	741

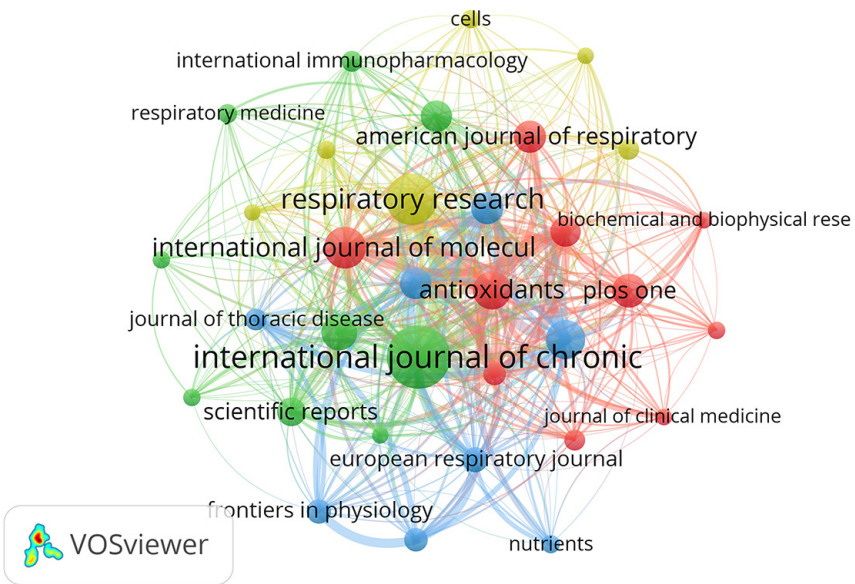

Figure 4 Visual representation of chronic obstructive pulmonary disease publications related to oxidative stress in academic journals.

lead to a closer collaborative relationship. The results show that the author groups with stable cooperative relations are mainly concentrated in the same country or region.

Barnes, Peter J. has close collaboration with Adcock, Ian M. with 37 articles, and Chung, Kian Fan with 21 articles, ranking them at positions 2 and 4 respectively among the top 10 authors in this field. It is noteworthy that both of these authors are affiliated with Imperial College London, indicating the significant contribution made by this university to the advancement of research in this area. Additionally, Irfan Rahman from the University of Rochester has published a total of 25 papers on nuclear factor erythroid 2-related factor 2 (Nrf2) and oxidative stress induced by cigarette smoke, securing the third position among these researchers who have conducted extensive investigations (23,24). Also, he maintains a close collaborative partnership with Hongwei Yao, Sundar IK., and Isaac K., collectively making outstanding contributions to the field of lung pathophysiology by advancing our understanding of sirtuin 1 and the Circadian molecular

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Table 3 Top 10 journals on the research

Rank	Journals	Counts	IF (2024)
1	*International Journal of Chronic Obstructive Pulmonary Disease*	69	2.7
2	*Respiratory Research*	51	4.7
3	*International Journal of Molecular Sciences*	38	4.9
4	*Free Radical Biology and Medicine*	35	7.1
5	*Antioxidants*	34	6
6	*Frontiers In Pharmacology*	30	4.4
7	*PLoS One*	28	2.9
8	*American Journal of Physiology-Lung Cellular and Molecular Physiology*	26	3.6
9	*American Journal of Respiratory Cell and Molecular Biology*	26	5.9
10	*American Journal of Respiratory and Critical Care Medicine*	25	19.3

IF, impact factor.

Table 4 Top 10 co-cited journals on the research

Rank	Co-cited journals	Counts	IF (2024)
1	*American Journal of Respiratory and Critical Care Medicine*	1,381	19.3
2	*European Respiratory Journal*	1,277	16.6
3	*Chest*	1,042	9.5
4	*Thorax*	998	9.0
5	*PLoS One*	942	2.9
6	*Respiratory Research*	910	4.7
7	*American Journal of Physiology-Lung Cellular and Molecular Physiology*	878	3.6
8	*American Journal of Respiratory Cell and Molecular Biology*	897	5.9
9	*Lancet*	759	98.4
10	*Free Radical Biology and Medicine*	750	7.1

IF, impact factor.

clock (25-28).

The top 10 co-cited authors and the frequency of their co-citations are presented in *Table 5*. A higher number of co-citations indicates greater objectivity, scientific rigor, and effectiveness in their publications, as well as recognition by fellow researchers in the same field (29). Notably, the most frequently cited author is still Barnes from the United Kingdom, who was cited 1,225 times in total. Rahman, Irfan is cited 791 times, while Barreiro, E. is cited 334 times. *Figure 5B* illustrates the network of co-cited author relationships, while the density of co-cited author influence in this domain is clearly shown in *Figure 5C*.

Analysis of related references

A document is referred to as a co-cited work when it is simultaneously cited by two or more other publications. The total number of citations serves as a measure of a paper's significance within a specific research domain (30,31). As shown in *Table 6*, the article "Oxidative Stress in COPD" by Kirkham *et al.*, published in *Chest* in 2013, holds the top position with 192 citations. This study highlighted that oxidative stress is not only pivotal in the pathogenesis of COPD but also in the progression of the disease (32). It is proposed that oxidative stress persists even after smoking cessation due to endogenous sources, such as

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Table 5 Top 10 productive authors and co-cited authors

Rank	Authors	Counts	Co-cited authors	Citations
1	Barnes, Peter J.	47	Barnes, Peter J.	1,225
2	Adcock, Ian M.	34	Rahman, Irfan	791
3	Rahman, Irfan	25	Barreiro, E.	334
4	Chung, Kian Fan	21	Ito, Kazuhiro	298
5	Vlahos, Ross	19	Kirkham, Pa	253
6	Zinellu, Angelo	19	Hongwei, Yao	251
7	Ito, Kazuhiro	18	Rabe, Kf	243
8	Hongwei, Yao	18	Hogg, Jc	222
9	Carru, Ciriaco	17	Macnee, W.	206
10	Pirina, Pietro	17	Churg, A.	193

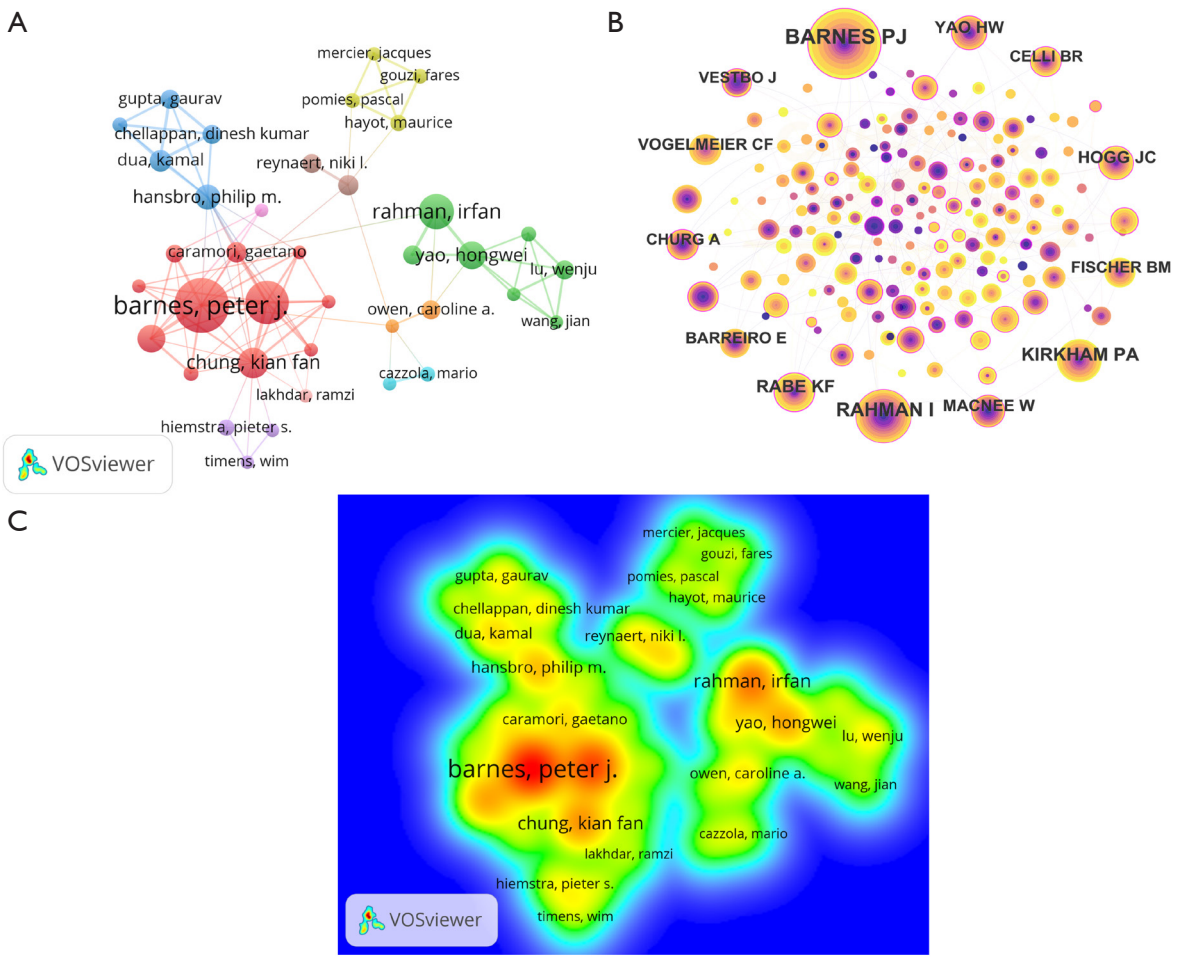

Figure 5 Visual representation of relevant authors and co-cited authors. (A) Visual mapping of author collaborations associated with oxidative stress in chronic obstructive pulmonary disease publications. (B) Visualization of co-cited authors in the research. (C) The density chart of authors in this field.

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Table 6 Top 10 co-cited publications

Rank	Cited reference	Citations	Author's country
1	Kirkham PA, 2013, Chest, V144, P266, doi 10.1378/Chest.12-2664	192	UK
2	Rabe Kf, 2007, Am J Resp Crit Care, V176, P532, doi 10.1164/Rccm.200703-456So	150	Germany
3	Rahman I, 2006, Eur Respir J, V28, P219, doi 10.1183/09031936.06.00053805	148	USA
4	Barnes Pj, 2016, J Allergy Clin Immun, V138, P16, doi 10.1016/J.Jaci.2016.05.011	110	UK
5	Hogg JC, 2004, New Engl J Med, V350, P2645, doi 10.1056/Nejmoa032158	108	Canada
6	Rangasamy T, 2004, J Clin Invest, V114, P1248, doi 10.1172/Jci200421146	98	USA
7	Barnes Pj, 2020, Redox Biol, V33, doi 10.1016/J.Redox.2020.101544	84	UK
8	Ito K, 2005, New Engl J Med, V352, P1967, doi 10.1056/Nejmoa041892	84	Japan
9	Vestbo J, 2013, Am J Resp Crit Care, V187, P347, doi 10.1164/Rccm.201204-0596Pp	82	UK
10	Drost Em, 2005, Thorax, V60, P293, doi 10.1136/Thx.2004.027946	79	UK

mitochondrial respiration. Furthermore, the limitations of current antioxidant treatment strategies are discussed, and novel treatment directions are suggested, including Nrf2 activators, superoxide dismutase mimics, nitrogen oxides, and myeloperoxidase inhibitors. Additionally, the potential for combination therapy is highlighted by considering antioxidants in combination with other drugs like anti-inflammatory agents, bronchodilators, antibiotics, and statins. A novel perspective is put forward suggesting that oxidative stress may lead to autoimmune responses through the generation of oxidatively modified proteins acting as neoantigens capable of triggering immune reactions.

Table 6 presents comprehensive information regarding the 10 most co-cited articles, including their respective citations and the corresponding author's country. Notably, five out of these ten highly cited publications originate from the United Kingdom, showcasing the exceptional quality of research output in this area by that nation. The reference co-occurrence network map is shown in *Figure 6A*. Utilizing the CiteSpace clustering function, *Figure 6B* demonstrates the application of co-citation analysis to explore topics within similar documents (33). The most prominent cluster ranking is #0, belonging to total alkaloids, followed by histone deacetylase, tobacco smoke, and sirtuins. Clusters results indicate they have close coherence with COPD and oxidative stress. Also, *Figure 6C* clearly illustrates the density of co-cited references within this field, we can intuitively see the influential authors in the field.

The Brust detection algorithm, created by Kleinberg, serves as a crucial analytical tool for capturing sudden surges in keywords or references within a specified time period (34). This feature enables the detection of literature popularity at various intervals, facilitating the prompt recognition of actively discussed concepts or topics, which in turn informs emerging research trends and developments in the domain (35). *Figure 6D* presents the top 25 references with the most notable citation bursts. The review article titled "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary", authored by Vestbo *et al.* (36), experienced the most extended burst period, lasting from 2013 to 2018. The first citation burst occurred in 2010, while the most recent one was noted in 2020 from an article titled "Oxidative Stress-Based Therapeutics in COPD", published in *Redox Biology* (37). This article primarily addressed the origins of oxidative stress and outlined fundamental strategies for its reduction in COPD. It explicitly states that targeting pulmonary oxidative stress presents a rational therapeutic approach but underscores the necessity for further exploration of more effective antioxidants. Apart from this, the review titled "Cellular Senescence as a Mechanism and Target in Chronic Lung Diseases", along with an article published in *Lancet* in 2018, titled "Prevalence and Risk Factors of Chronic Obstructive Pulmonary Disease in China (the China Pulmonary Health [CPH] Study): A National Cross-Sectional Study", is currently experiencing a surge in citations. Both articles showed us the perniciousness of COPD, which has become an innegligible public health problem, and discussed risk factors/pathogenesis while emphasizing further research on therapeutic targets for COPD (38,39).

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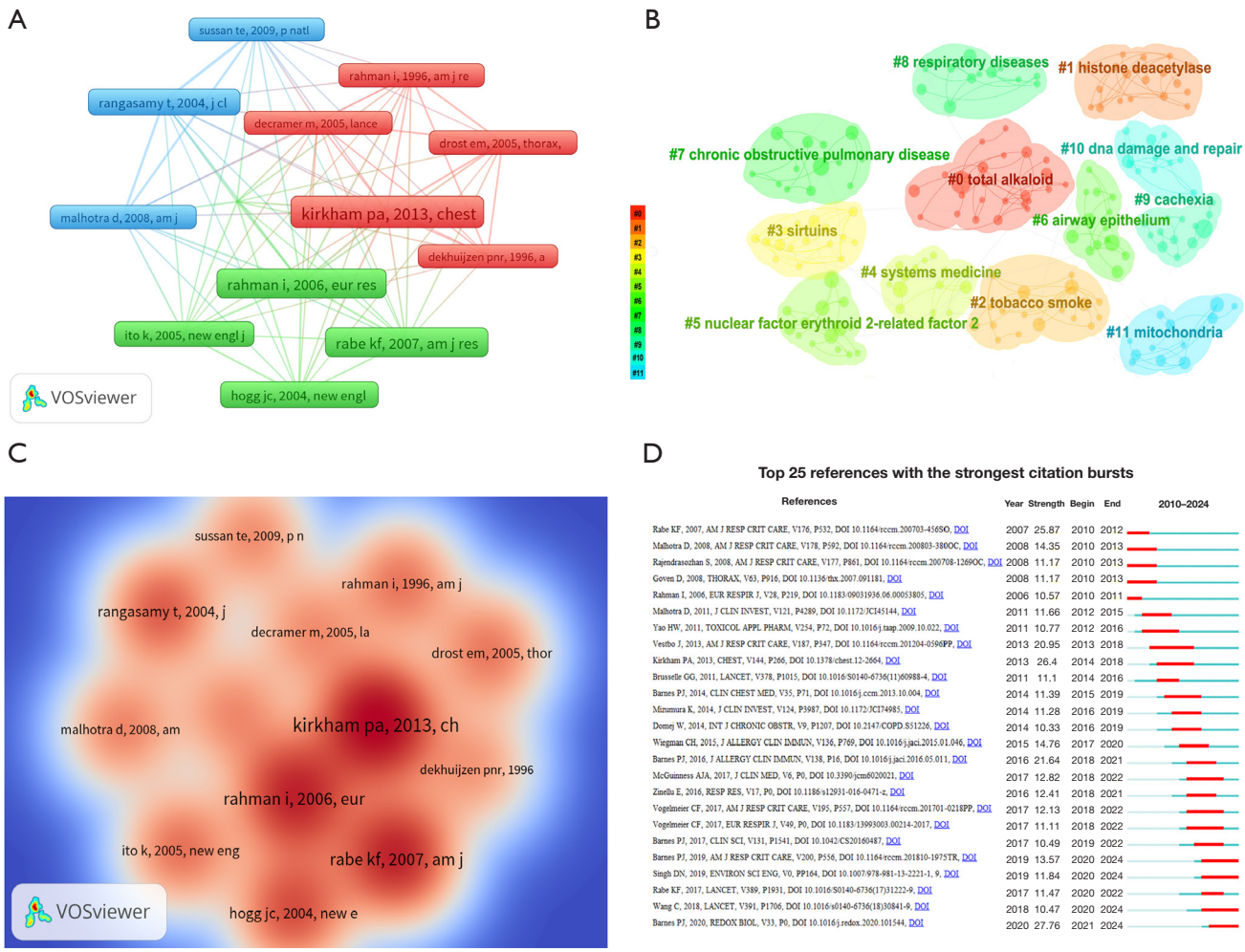

Figure 6 Visual representation of related reference. (A) Network map of reference co-occurrence. (B) Clustering map of reference co-occurrence. (C) The density chart of reference in this field. (D) Top 25 references with the highest citation bursts.

Analysis of keywords

Keywords function as a concise overview of the article's subject matter. Analyzing these keywords enables a comprehensive understanding of the current research landscape, highlights primary areas of focus, and suggests possible future pathways in the study of oxidative stress in COPD. *Figure 7A* presents a diagram illustrating the network of keyword contributions, while *Table 7* lists the 20 keywords. Notably, the terms "oxidative stress", "chronic obstructive pulmonary disease", and "inflammation" appeared respectively with frequencies of 591, 448, and 277 mentions, establishing them as the three most significant keywords. This finding suggests a strong interrelationship between oxidative stress and inflammation in COPD research.

Following the clustering of all keywords, we generated a cluster graph depicted in *Figure 7B*. It is worth noting that cigarette smoke not only ranks seventh among these eleven topics but also appears fourth most frequently throughout this study with a total occurrence of 148 times. Cigarette smoke extract is considered one of the key factors contributing to COPD pathogenesis. Interestingly enough, lung cancer ranked third among eleven groups. Several pieces of research have indicated that lung cancer often impacts patients with COPD (40), and they all have strong connections to oxidative stress and cigarette smoke (41,42). The research has shown that grape seed proanthocyanidin can improve COPD and lung cancer induced by cigarette smoke extract by inhibiting oxidative stress-induced epithelial apoptosis (43).

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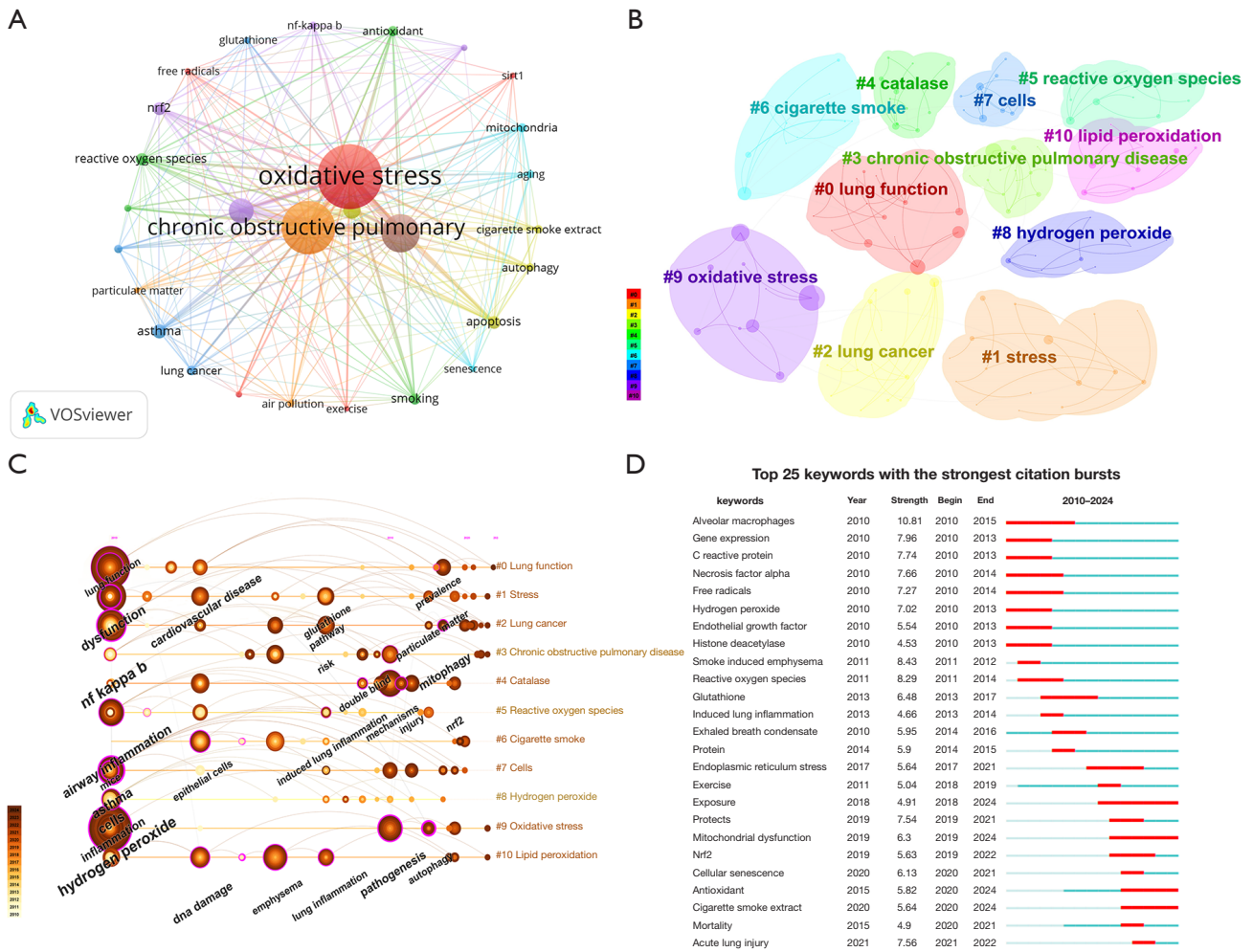

Figure 7 Visual representation of keyword in this filed. (A) Network map of keyword co-occurrence. (B) Keyword clustering map. (C) The timeline diagram of keyword clusters. (D) Top 25 keywords with the strongest citation bursts.

Utilizing the keyword cluster graph, we create a timeline graph for keywords (*Figure 7C*), which emphasizes numerous terms within the specific cluster. The graph illustrates that research concerning Nrf2, particulate matter, autophagy, and mitophagy has emerged as prominent and cutting-edge topics in this area since 2020 and remains relevant. In *Figure 7D*, we established the top 25 outbreak keywords, which identify the research hot spots in this field at different time points through the rapid outbreak of the research topic in a specific time (44). Mitochondrial dysfunction, antioxidants, and cigarette smoke extract are now hot topics in the research of oxidative stress in COPD.

The imbalance between oxidants and antioxidants is a key factor in the development of COPD, making the quest for effective antioxidants a focal point and trend in its treatment (45). Various antioxidants have been investigated in several clinical trials, demonstrating their ability to decrease acute exacerbations among COPD patients. Mimetics of superoxide dismutase and glutathione peroxidase, such as AEOL 10150 and ebselen, have demonstrated efficacy in animal studies, though they remain underexplored in human COPD patients (46). NADPH oxidase inhibitors (47), such as apocynin and setanaxib, are under development and may be useful for COPD treatment.

Investigating mitochondrial dysfunction and its regulation will deepen our understanding of the molecular mechanisms involved in chronic lung diseases, potentially leading to novel therapeutic strategies. Targeting impaired mitochondria could serve as a promising approach to mitigate the progression and worsening of COPD.

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Table 7 Top 20 keywords with the highest frequency

Rank	Keywords	Counts
1	Oxidative stress	591
2	Chronic obstructive pulmonary disease	448
3	Inflammation	277
4	Cigarette smoke	148
5	Emphysema	88
6	Asthma	67
7	Apoptosis	58
8	Nrf2	58
9	Reactive oxygen species	52
10	Smoking	46
11	Antioxidant	41
12	Lung cancer	40
13	Mitochondria	36
14	Autophagy	33
15	Biomarkers	30
16	Cigarette smoke extract	30
17	Aging	28
18	Cardiovascular disease	26
19	Nf-kappa B	25
20	Air pollution	24

Moreover, exploring mitochondria-targeting antioxidants like mitoQ and SkQ1 (48), currently undergoing clinical trials for other chronic ailments, may also be a valuable avenue of research in relation to COPD. Multiple studies have demonstrated a direct correlation between skeletal muscle dysfunction in individuals with COPD and mitochondrial dysfunction (49,50).

Numerous studies have established a clear link between skeletal muscle dysfunction in individuals with COPD and mitochondrial dysfunction (51-54). Cigarette smoke exposure is widely recognized as a major factor in triggering and exacerbating COPD, leading to excessive inflammation in the airways, alveoli, and capillaries (55-57). Research indicates that complement component 3, produced locally, helps protect human bronchial epithelial cells from oxidative stress caused by cigarette smoke, thus preventing prolonged apoptosis (58). This finding suggests a potential new mechanism in the development of COPD.

Discussion

In this study, we used five scientific tools to conduct bibliometric and visual analysis of 1,748 papers published in the field of COPD and oxidative stress between January 1, 2010, and July 25, 2024. Our study systematically assessed the current research status and potential future research directions in the domain of oxidative stress and COPD. To our knowledge, this represents the first comprehensive bibliographic review conducted in this specific area. Through a combination of quantitative and qualitative analyses, we identified emerging research trends and changes that will be discussed in detail in the following sections to offer a thorough overview of our findings.

General information

Based on the analysis of the yearly growth trend in publications within this field indicates a steady rise in their quantity, particularly since 2021, when it is stable at over 150 per year. The high R^2 value of 0.9047 suggests that research on oxidative stress in COPD is still emerging and holds significant potential for further development. China leads globally with 490 publications in this area, followed by the USA and the UK with 325 and 149 publications respectively.

While significant collaborative efforts have been made by countries like the USA, China, Britain, and Italy in this field, *Figure 3* illustrates that certain countries still engage in independent academic research. This points to potential academic barriers that impede international collaboration, such as differences in research methodologies, lack of funding, and institutional or bureaucratic challenges. Overcoming these obstacles could promote stronger global cooperation and innovation, driving further progress in COPD research and contributing to worldwide scientific advancement.

Barnes, Peter J. from Imperial College London, a distinguished scholar in the field, ranks first among top authors and co-cited authors with 47 papers and an impressive citation count of 1,225 citations, showcasing his significant contributions to this area of study. The *International Journal of Chronic Obstructive Pulmonary Disease* stands out as the most prolific journal within this domain, with a total publication count of 69 papers published so far.

Knowledge base

Highly cited literature is often the cornerstone of a field's

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development and has a significant impact on the field. By analyzing the top 10 cited literature after 2000, we gained insight into the relationship between COPD and oxidative stress.

The characteristics of small airway obstruction in COPD were examined as early as 2004 by Hogg and colleagues (59) who assessed small airways in surgically resected lung tissue obtained from 159 COPD patients, utilizing the GOLD classification to explore the evolution of airway obstruction associated with this condition. Their analysis employed Poisson regression to evaluate the number of airways infiltrated with inflammatory cells, revealing that the progression of COPD correlates with an increased presence of polymorphonuclear neutrophils, macrophages, CD4 T-cells, and various lymphocyte subtypes. Additionally, the accumulation of inflammatory mucus in the lung lumen and the infiltration of both innate and adaptive immune cells into the lung wall contribute to the formation of lymphoid follicles, which further exacerbate the advancement of COPD. In the same year, Rangasamy (60) and his team in the United States investigated the Nrf2 signaling pathway, identifying it as a crucial factor influencing susceptibility to emphysema caused by cigarette smoke. They discovered that a deficiency in Nrf2 results in heightened alveolar inflammation, increased apoptosis of alveolar septal cells, and greater oxidative stress within the alveoli, ultimately leading to more severe emphysema following cigarette smoke exposure. Their research indicated that the genetic knockdown of Nrf2 heightened the vulnerability of mice to emphysema induced by cigarette smoke. Furthermore, through microarray analysis, they characterized the expression of nearly 50 Nrf2-dependent antioxidant and cytoprotective genes in the lungs, suggesting that these genes may work synergistically to mitigate oxidative stress and inflammation resulting from cigarette smoke. The activity of the Nrf2 pathway may significantly influence the likelihood of developing cigarette smoke-induced emphysema by enhancing antioxidant defenses and decreasing both lung inflammation and alveolar cell apoptosis. This research lays a robust groundwork for future studies aimed at upregulating and activating Nrf2 as a potential therapeutic strategy for COPD, indicating that Nrf2 activators could represent a promising treatment option for this disease.

In 2005, Drost *et al.* (61) explored the link between oxidative stress and airway inflammation during acute exacerbations of COPD. Their findings indicated that increased oxidative stress occurs in the airways of patients with COPD, particularly during severe or very severe stages, and is correlated with a heightened influx of neutrophils and elevated levels of interleukin (IL)-8. The same year, Ito and his team (62) conducted statistical experiments revealing that histone deacetylase (HDAC) serves a critical function in suppressing the production of pro-inflammatory cytokines by alveolar macrophages. They also identified a positive correlation between HDAC reactivity and the severity of the disease. It is important to highlight that HDAC not only inhibits gene transcription but also directly influences the nuclear activity of key transcription factors like nuclear factor-k-gene binding (NF-kB). NF-kB is a central player in oxidative stress in COPD, capable of being activated by various extracellular stimuli. It is universally expressed in cells, where it regulates the induction of inflammatory genes and also amplifies the activity of other cell-specific and signaling-specific transcription factors.

In 2006, Rahman (63) and colleagues conducted a study on oxidative stress and redox regulation of lung inflammation in COPD patients. This study offered an extensive review of the relationship between NF-kB, oxidative stress, and COPD. Rahman demonstrated that in unstimulated cells, NF-kB exists in the cytoplasm in a non-DNA-bound state, but upon activation, it translocates to the nucleus. In this context, NF-kB attaches to the promoter regions of particular target genes, resulting in the activation of inflammatory mediators including monocyte chemoattractant protein-1 (MCP-1), IL-8, and tumor necrosis factor-alpha (TNF-α). These mediators then attract and activate additional inflammatory cells, worsening lung inflammation. Furthermore, oxidative stress not only initiates the transcription of pro-inflammatory mediators regulated by NF-kB through the activation of NF-kB-a kinase or by enhancing the recruitment and activation of transcriptional co-activators, but it also increases the activity of the NF-kB pathway. This creates a positive feedback mechanism that perpetuates and escalates the inflammatory response. Rahman's research also emphasized that the release of reactive oxygen species (ROS) from activated neutrophils, alveolar macrophages, eosinophils, and epithelial cells plays a significant role in contributing to oxidative stress. When generated near cellular membranes, ROS can lead to lipid peroxidation. The resultant compounds, including malondialdehyde, 4-hydroxy-2-nonenal, acrolein, and F2-isoprostanes, are involved in cellular oxidative stress processes and mediate inflammatory responses within the lungs. Additionally, ROS has the potential to initiate the oxidation of proteins, DNA,

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and lipids via secondary metabolic byproducts. This cascade of reactions can lead to direct lung injury, impact a variety of cellular responses, and alter mechanisms of alveolar repair and immune regulation in the lungs. ROS also has the ability to influence the extracellular matrix and vascular remodeling, promote mucus production, trigger apoptosis, and modulate cell proliferation. All of these results highlight the pivotal role of ROS in the broader process of oxidative stress.

In 2007, Rabe (64) and colleagues published a GOLD Executive Summary, which provided the most current insights into COPD for healthcare professionals, organizations, and the general public, along with tailored recommendations for prevention strategies and effective management.

In 2013, Kirkham (32) and colleagues published a review in *Chest* titled "Oxidative Stress in COPD," which garnered the highest citation count due to its comprehensive analysis of how oxidative stress is produced and mitigated in the lungs, as well as the shortcomings of the antioxidant strategies prevalent at that time. The review emphasizes that prolonged exposure to cigarette smoke or certain biofuels can induce oxidative stress by disrupting the body's antioxidant defenses, rendering them ineffective against ROS. Notably, even after patients with COPD cease exposure to these external factors, they do not experience remission, indicating that intrinsic factors also play a role in sustained oxidative stress. Kirkham's findings suggest that the inadequacy of antioxidant treatments in COPD may stem from their inability to specifically target cellular compartments that require these agents the most. Additionally, the potency of the antioxidants used, along with insufficient dosages and administration frequency in clinical trials, may have contributed to the strategy's failure at that time. This underscores the need for advancements in developing broad-spectrum small-molecule antioxidants that possess enhanced bioavailability and efficacy. In the same year, Vestbo *et al.* (36) revised the GOLD Executive Summary. They introduced distinct sections addressing the management of comorbidities and the treatment of COPD when comorbid conditions are present, highlighting the significant impact of these comorbidities on patient prognosis. Conditions such as cardiovascular disease, osteoporosis, and depression frequently accompany COPD and are often underdiagnosed, negatively affecting health status and outcomes. Furthermore, lung cancer is prevalent among COPD patients and is recognized as the leading cause of death in those with mild forms of the disease. The abstract clarifies that the existence of comorbidities should not modify the approach to treating COPD; rather, these conditions should be managed independently of the COPD diagnosis. Additionally, the updated summary includes a new section dedicated to acute exacerbations of COPD, outlining treatment objectives aimed at minimizing the impact of ongoing exacerbations and preventing future occurrences. Short-acting inhaled β2 agonists, with or without short-acting anticholinergics, are identified as preferred bronchodilators for addressing acute exacerbations, reflecting the substantial recommendations for managing the acute phase of COPD at that time.

Oxidative stress was found to play a key role in COPD-associated inflammation and may exacerbate comorbidities such as vascular disease, diabetes, and osteoporosis in Barnes' 2016 study of the mechanisms of inflammation in patients with COPD (65). In this review, Barnes discussed the inflammatory nature of COPD patients, proposing potential molecular mechanisms that could serve as new targets for more effective anti-inflammatory therapies in the future. He emphasized the importance of identifying patient phenotypes that respond optimally to specific treatments, along with the development of biomarkers to identify these therapeutic phenotypes as crucial areas for future research. Four years later, in 2020, Barnes (37) and colleagues released a follow-up review titled "Oxidative Stress-Based Therapeutics in COPD." This paper underscored oxidative stress as a central mechanism contributing to COPD and provided an extensive overview of its detrimental effects on lung health. Barnes concluded that oxidative stress triggers various signaling pathways with redox-sensitive molecular targets, which in turn leads to the release of numerous inflammatory mediators in the lungs of COPD patients. This process heightens inflammation, promotes fibrosis and emphysema, leads to corticosteroid resistance, accelerates the aging of lung tissue, induces DNA damage, and contributes to the production of autoantibodies. Consequently, he argued that targeting oxidative stress through antioxidants or boosting the body's natural antioxidant defenses represents a viable strategy for addressing the underlying causes of COPD. The review evaluated the potential and limitations of various antioxidant approaches, including sulfhydryl antioxidants, dietary antioxidants, antioxidant mimetics, superoxide dismutase mimetics, NADPH oxidase inhibitors, NOX inhibitors, and Nrf2 activators, ultimately concluding that mitochondria-targeted antioxidants show the greatest promise for COPD treatment.

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Furthermore, an analysis of the top 10 cited articles regarding oxidative stress in COPD indicated that elevated oxidative stress is vital for chronic inflammation, disease progression, and exacerbation, adversely affecting lung function. However, the development of pharmacological interventions targeting this pathway is currently insufficient, making the targeting of oxidative stress a vital focus for future drug development efforts.

Emerging topics

The keyword burst shows that the research focus on oxidative stress in COPD has changed from gene expression and necrosis factor alpha turns to exposure, cigarette smoke extract, mitochondrial dysfunction, and antioxidant.

The occurrence of exposure bursts is primarily associated with the influences of prolonged exposure to the source of ROS, including air pollution and cigarette smoke, on the progression of COPD. This exposure is fundamentally linked to both the onset and worsening of COPD. Researches have indicated that higher levels of oxidative stress markers, detectable in the respiratory tracts of COPD patients, result from extended exposure to both external and internal oxidative stress sources. This accumulation ultimately results in irreversible lung damage (66-68). In 2020, a research team led by Xue (69) investigated the connection between lung cancer, COPD, and telomere length in Xuanwei City, China. Their findings revealed a positive correlation between lung function and telomere length, coupled with a negative correlation between lung function and environmental exposure when comparing COPD patients with a control group. This suggests that alterations in telomere length due to environmental factors significantly influence the development and aggravation of COPD, highlighting the close relationship between environmental exposure and the disease.

Cigarette smoke, acknowledged as a primary contributor to environmental exposure and a significant causative factor in COPD, has prompted many researchers to use it as a focal point for investigating oxidative stress in this condition. A wealth of studies has documented that cigarette smoke comprises harmful substances, including polycyclic aromatic hydrocarbons, nitric oxide, hydrogen peroxide, and ROS, all of which can instigate oxidative stress, exacerbate lung inflammation, and result in damage and remodeling of lung tissue. When chemicals from cigarette smoke come into contact with alveolar epithelial cells and alveolar macrophages, they produce ROS (70). Then the accumulation of these ROS often surpasses the clearance capacity of the endogenous antioxidant systems present in alveolar cells and macrophages, culminating in an antioxidant system imbalance. This disruption can cause cellular injury, compromise the alveolar epithelial barrier, hinder cellular autophagy, and lead to the buildup of intracellular damage, which ultimately results in an irreversible decline in lung function.

Once COPD is established, quitting smoking can't alleviate the persistent oxidative stress or stop the advancement of the disease. Research has indicated that grape seed proanthocyanidin extract can modulate apoptosis in epithelial cells by inhibiting oxidative stress in COPD patients (41). Recently, Kaur (56) and colleagues published an article suggesting that guggulsterone may offer protective effects against lung inflammation associated with COPD induced by cigarette smoke by modulating key molecular factors. This discovery represents a significant advancement in the exploration of therapeutic strategies for COPD.

Mitochondria are important sites for producing ROS through oxidative phosphorylation. Damage to these organelles leads to an overproduction of ROS, resulting in heightened oxidative stress, which compromises the antioxidant system in the body. This disruption diminishes the efficacy of antioxidant defenses, aggravates various programmed cell death pathways, and contributes to irregularities in lipid metabolism. These processes ultimately result in dysfunction of the airway epithelium and the onset of airway abnormalities associated with COPD. Furthermore, there exists a reciprocal relationship between oxidative stress and mitochondrial dysfunction. Specifically, oxidative stress can induce mitochondrial dysfunction by altering mitochondrial structure and morphology, as well as damaging various mitochondrial proteins. In return, mitochondrial dysfunction leads to the accumulation of impaired mitochondria and inhibits autophagy, which exacerbates oxidative stress and heightens inflammatory responses (71). Considering that dysfunction of the mitochondria is a major contributor to endogenous ROS in COPD, employing aimed mitochondrial antioxidants represents a potentially promising therapeutic strategy in antioxidant treatments for this condition. Mitochondria-targeted (mt) antioxidants, particularly those derived from ubiquinone, have demonstrated a capacity to concentrate within mitochondria at levels 50–100 times greater than traditional antioxidants in various aging animal models (72). Despite this, clinical trials in humans examining the

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effectiveness of mt antioxidants for COPD are still underway, and no results have been published thus far. Notably, research indicates that transferring mitochondria mesenchymal stem cells derived from induced pluripotent stem cells to airway epithelial cells can reduce oxidative stress resulting from cigarette smoke and lessen lung injury and inflammation triggered by lipopolysaccharides (LPS) and allergens (73), which provides a new idea for further digging into the study of the treatment of COPD from the start of mitochondrial dysfunction.

Oxidative stress is pivotal in the progression of COPD, so controlling and attenuating both local and systemic oxygen bursts associated with COPD through antioxidant therapy is a viable pathway. A summary of highly cited literature in COPD and oxidative stress research as well as keyword burst analysis reveals that antioxidant research continues to be the focus of today's study in this domain. Antioxidants are essential in alleviating oxidative stress as they efficiently neutralize harmful free radicals, reduce inflammatory responses, improve lung function, and decelerate the disease's progression in COPD patients. A notable relationship exists between decreased intrapulmonary antioxidant levels and the decline in lung function among individuals with COPD (30). Various antioxidants, such as thiols, dietary antioxidants, nitrogen oxide inhibitors, peroxidase inhibitors, and mitochondria-targeted antioxidants, have been recognized. Specific antioxidants like N-acetylcysteine, carbocisteine, and Erdosteine have been evaluated in COPD patients, demonstrating a reduction in the frequency of acute exacerbations, albeit with limited enhancements in lung function and life quality. Additional *in vitro* research has indicated that dietary polyphenols, including resveratrol and curcumin, may inhibit the activation of NF-kB triggered by cigarette smoke and oxidative stress, histone acetylation, and the release of pro-inflammatory cytokines, while also restoring glucocorticoid function via HDAC activity upregulation (74). Resveratrol (75,76), a strong antioxidant commonly found in wine, is a stilbene polyphenol recognized for its capacity to suppress ROS produced by inflammatory cells and effectively scavenge free radicals; it continues to be widely studied in scientific literature. Furthermore, it is considered a promising antioxidant for COPD, potentially stimulating the synthesis of endogenous antioxidants through the ROS-related activation of Nrf2. However, there is a category of antioxidants that, despite showing positive outcomes in animal studies, have exhibited limited effectiveness in clinical trials, likely due to rapid degradation from the excessively high oxidative stress levels seen in the lungs of COPD patients. To sum up, no particularly effective antioxidants are currently available for clinical application in mitigating COPD, making the development of innovative and effective antioxidants an active area of research. It's significant to mention that natural products have historically been acknowledged as rich sources for potential drug candidates due to their natural antioxidant capabilities, leading researchers to explore synthetic natural antioxidants as therapeutic options to slow the progression of COPD. Relevant researches have indicated that micronutrients like vitamin C, vitamin E, lycopene, flavonoids, and β-carotene possess remarkable properties to combat inflammation resulting from oxidative stress (76-78). Consequently, a diet abundant in these micronutrients, including fruits, vegetables, and nuts, may prove effective in mitigating inflammation induced by oxidative stress and preventing COPD onset. Numerous scientific investigations have highlighted that herbs offer distinct benefits in treating respiratory ailments due to their intrinsic properties and potential therapeutic effects (79-81). For instance, Tang has been found to enhance Nrf2 expression, inhibiting ROS production and lessening lung injury, while licorice demonstrates anti-inflammatory and antioxidant abilities, which may alleviate lung damage by modulating Nrf2 and NF-kB signaling pathways (82).

To summarize, while the significant impact of oxidative stress on the progression of COPD is well-established, and antioxidant-targeting strategies for COPD management are validated, existing antioxidant treatments for oxidative stress in COPD exhibit limited effectiveness in halting the disease or sufficiently reversing its progression. As oxidative stress continues to exacerbate the health status of COPD patients, leading to an increasing healthcare burden, there is an urgent need for the development of precision-targeted antioxidants that can effectively engage specific cellular compartments.

Limitations

The utilization of visual analysis tools can facilitate a comprehensive understanding of structural changes and trends in oxidative stress studies in COPD. Nonetheless, it is essential to recognize certain limitations inherent in this research. First, the bibliometric analysis software requires strict criteria and standards concerning data quality; hence, the search was confined to English-language publications sourced from core datasets within the Web of

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Science database. As a consequence, only two categories of publications (articles and review articles) were considered, which may have led to the omission of pertinent studies. Additionally, biases may exist during the manual literature selection process.

Conclusions

Overall analysis indicates that oxidative stress acts as an essential character in the development of COPD. The volume of publications concerning oxidative stress and COPD has consistently increased over time. On the whole, noteworthy contributions in this research area have been made by some prominent countries, such as China, the USA, and the UK, which have published numerous papers in this field. Imperial College London stands out with the highest publication count, while Barnes, Peter J., from this institution, has significantly contributed to the field with the most published and cited articles. Antioxidant therapy, cigarette smoke, and mitochondrial dysfunction are research hotspots in COPD disease. The development of novel and effective antioxidants targeting oxidative stress for COPD treatment is a trend of future research.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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