Heliyon 9 (2023) e17075

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research Article

A scientometrics and visualization analysis of oxidative stress modulator Nrf2 in cancer profiles its characteristics and reveals its association with immune response

Song-Bin Guo [a,b,1], Sheng Du [c,1], Ke-Yu Cai [d,e,1], Han-Jia Cai [f], Wei-Juan Huang [g,**], Xiao-Peng Tian [a,b,*]

[a] Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, 510060, PR China
[b] State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, 510060, PR China
[c] State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510120, PR China
[d] Department of Colorectal and Anal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, PR China
[e] Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, Guangdong Institute of Gastroenterology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, PR China
[f] The Second Clinical Medical College, Guangzhou Medical University, Guangzhou, 511436, PR China
[g] Department of Pharmacology, College of Pharmacy, Jinan University, Guangzhou, 510632, PR China

ARTICLE INFO

Keywords:
Nrf2
Oxidative stress
Immune response
Cancer
Scientometric
Visualization

ABSTRACT

Background: Nrf2, an essential and fascinating transcription factor, enjoys a dual property in the occurrence and development of inflammation and cancer. For over two decades, numerous studies regarding Nrf2 in cancer have been reported, whereas there is still a lack of a scientometrics and visualization analysis of Nrf2 in cancer. Hence, a scientometric study regarding the oxidative stress modulator Nrf2 was implemented.
Methods: After the quality screening, we defined 7168 relevant studies from 2000 to 2021. CiteSpace, VOSviewer, R software, and GraphPad Prism were used for the following scientometric study and visualization analysis, including field profiles, research hotspots, and future predictions.
Results: The total number of publications and citations are 1058 and 54,690, respectively. After polynomial fitting curve analysis, two prediction functions of the annual publication number ($y = 3.3909x^2 - 13585x + 1$ E+07) and citation number ($185.45x^2 - 743669x + 7$ E+08) were generated. After scientometric analysis, we found that Biochemistry Molecular Biology correlates with Nrf2 in cancer highly, and Free Radical Biology and Medicine is a good choice for submitting Nrf2-related manuscripts. The current research hotspots of Nrf2 in cancer mainly focus on cancer therapy and its cellular and molecular mechanisms. "antioxidant response element (87.5)", "gene expression (43.98)", "antioxidant responsive element (21.14)", "chemoprevention (20.05)", "carcinogenesis (19.2)", "cancer chemoprevention (18.45)", "free radical (17.15)", "response element (14.17)", and "chemopreventive agent (14.04)" are important for cancer therapy study.

* Corresponding author. Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, 510060, PR China.
** Corresponding author.
E-mail addresses: wjhuang@jnu.edu.cn (W.-J. Huang), tianxp@sysucc.org.cn (X.-P. Tian).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e17075
Received 21 February 2023; Received in revised form 2 June 2023; Accepted 6 June 2023
Available online 7 June 2023
2405-8440/

In addition, "glutathione-*S*-transferase (47)", "keap1 (15.39)", and "heme oxygenase 1 gene (24.35)" are important for inflammation and cell fate study. More interestingly, by performing an "InfoMap" algorithm, the thematic map showed that the "immune response" is essential to oxidative stress modulator Nrf2 but not well developed, indicating it deserves further exploration.
Conclusion: This study revealed field profiles, research hotspots, and future directions of oxidative stress modulator Nrf2 in inflammation and cancer research, and our findings will offer a vigorous roadmap for further studies in this field.

1. Introduction

Many factors can damage DNA, proteins, or lipids in cells directly or indirectly, such as exogenous drugs, endogenous reactive oxygen species or free radicals. To counteract such detrimental factors, our organism has developed some sophisticated tactics, such as oxidative stress response, to mitigate the cellular impairment caused by these impacts [1–5]. During this process, the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is considered a significant modulator, maintaining the cellular redox balance by expressing antioxidant proteins [6]. Actually, reactive oxygen species and free radicals possess a dual nature in tumor formation or progression [7,8]. On the one hand, the accumulation of reactive oxygen species or free radicals increases the risk of tumor formation and malignant transformation by raising the rate of gene mutation. On the other hand, reactive oxygen species or free radicals also significantly function in cancer cell death [9–11]. With such a dual nature, reactive oxygen species and free radicals award Nrf2 an attractive but equivocal property in cancer cell biology [12]. Moderate activation of the Nrf2 signaling pathway is one of the most critical strategies to prevent cancerogenesis. A large number of cancer chemopreventive compounds targeting Nrf2 have been reported, such as Oltipraz [13], Sulforaphane [14], Curcumin [15,16], Resveratrol [17,18], and so on. Substantial studies have shown that, in various cancers cells, the activation of the Nrf2 signaling pathway promotes cell proliferation [19], prevents cell apoptosis [20], enhances the self-renewal capacity of cancer stem cells (CSC) [21], as well as, worse still, enhances the chemo-resistance [22] and radio-resistance [23] of cancer cells [24,25]. Therefore, blocking the Nrf2 signaling pathway is a potential therapeutic weapon in cancer campaigns, especially for cancer with high Nrf2 expression. Extensive Nrf2 inhibitors have also been reported, such as Luteolin [26], Retinoic acid [27], ML385 [28], Trigonelline [29], Brusatol [30,31], and so on [32,33].

Since the first proposal and definition by Otlet and Nalimov, the theory, technique, and application of scientometrics have been continuously expanded and ameliorated with the enormous effort of investigators [34]. Scientometrics is an interdisciplinary subject that, taking scientific knowledge carrier and its relevant information as a dataset, conducts a qualitative and quantitative analysis of their quantity, structure, distribution, interreaction, and component evolution using mathematical and statistical methods [35]. Scientometrics was born from the intersection of library science and informatics and has recently been extensively wielded in many medical domains, such as basic medicine, clinical medicine, and healthcare [36–40]. By quantitatively assessing authors, countries, affiliations, journals, and research categories in a given domain, scientometrics could thus uncover the productivity, impact, contribution, distribution, and collaboration of the academic research components in the field [41]. In addition, by analyzing literature and database features, scientometrics assists us in understanding the development textures and frontiers of relevant academic territory through data visualization in short order, thus providing reliable evidence for our current experimental strategies and financing decisions [42]. More interestingly, by analyzing the current research situation and development trends in the field, scientometrics could predict the next potential research theme hotspot [43].

However, there is still a lack of a scientometrics and visualization analysis of oxidative stress modulator Nrf2 in cancer. Hence, the purpose of this study was to uncover the current situations, development textures, and theme hotspots of oxidative stress modulator Nrf2 in cancer as well as provide some predictions in this domain.

2. Methods

2.1. Research theme identification and data source

To select and filter the research theme, "Nrf2″ and "cancer" were initially used to retrieve and assess the size of the data pool, and those with thousands of publications were considered suitable for further scientometric analysis. Then, the keywords "Nrf2″ and "scientometric* or bibliometric*" were used to evaluate previous relevant studies to confirm the value of the study.

To ensure the quality and reliability of the data, the Thomson-Web Reuter's of Science Core Collection (WOSCC), a globally dominant knowledge database with universally recognized comprehensiveness and authenticity, was selected for our data pool.

2.2. Search strategy

To ensure the comprehensiveness of the included cancer types and Nrf2-related expressions, we searched, analyzed, and summarized a large amount of literature in the field (7 hundred articles), and in addition, we also made use of the MeSH database and finally identified 16 terms and their derivatives to encompass all cancer types and 15 terms to encompass Nrf2-related expressions. The search query was "TS=(tumor* or tumor* or neoplas* or cancer* or sarcoma* or carcinoma* or adenocarcinoma* or choricarcinoma* or melanoma* or teratoma* or lymphoma* or myeloma* or leukemia* or leukemia* or malignan* or metastat*) AND TS=("nrf2" or “nuclear factor erythroid 2 related factor 2" or “nuclear factor-erythroid 2-related factor 2" or “nuclear factor erythroid-2 related factor 2" or “nuclear factor erythroid 2-related factor 2" or “nuclear erythroid 2-related factor 2" or “nuclear factor-erythroid 2 p45-related factor 2" or “nuclear factor erythroid-derived 2-like 2" or “nuclear factor (erythroid-derived 2)-like 2" or “nuclear factor, erythroid 2-like 2" or “NF-E2-related factor 2" or “NF-E2 p45-related factor 2" or “nuclear factor-E2-related factor 2" or “nuclear factor E2-related factor 2" or “nuclear factor erythroid 2 (NF-E2)-related factor 2")". The search symbol "*" represents any letter or no letter. The publication year was limited from 2000 to 2021. The preliminary retrieval yielded 7613 items containing all types of documents, such as articles, reviews, meetings, patents, books, letters, abstracts, etc. To ensure the quality and reliability of the data, articles and reviews with rigorous peer review and comprehensive document content were selected to perform the subsequent analysis.

2.3. Data collection

Numerous Nrf2-related data were extracted and quantified from all indicated documents and then saved in Microsoft Excel, including total publication number, total citation number, average publication number, average citation number, citation number without self-citation, h-index, publication year, references, authors, countries, affiliations, journals, and keywords. To avoid errors and bias in data collection, we ensured that one author was the primary collector and arranged for two other authors to double-check the data.

2.4. Scientometrics and visualization analysis

The data was then performed further visualization analysis using GraphPad Prism 7.0, VOSviewer 1.6.18 (0), CiteSpace 6.1. R2, and R 4.2.2.

The publication and citation number are standard metrics utilized in scientometrics. As the two core metrics for evaluating academic performance, the publication number indicates productivity, and the citation number denotes impact.

The h-index is an indicator for evaluating scholars’ academic contributions and predicting future research achievements. The h-index indicates that a given scholar has at most h papers cited at least h times each, subtly linking productivity and impact. In addition, it could be used to evaluate the academic achievements of a country, affiliation, or journal.

The Global Citation Score (GCS), namely citation number, is an essential metric for evaluating the contribution of an article to a knowledge field, and a higher GCS proves that the world’s scientists are more interested in it. The polynomial fitting curve model was generated to predict the annual publication number or GCS. The variable f (x) denotes the annual publication number or GCS, and x denotes the year of publication.

VOSviewer was utilized for co-authorship and co-occurrence analysis, thus constructing and generating visualization networks [44, 45]. In the visualization network, the thickness of the line indicates the strength of the relationship, the magnitude of the node indicates the publication number, and the color of the node denotes different clusters or periods. CiteSpace was utilized to perform keyword citation burst analysis, achieving a visualization assessment of previous research hotspots in the knowledge domain [46,47]. The status and hotspot prediction of research themes were performed using the “R-bibliometrix” package. More specifically, first of all, the Java environment is necessary for VOSviewer and CiteSpace to run. For VOSviewer, click on the “Create” button to create a map based on bibliographic data, then click on the “Next” button, click “Read data from bibliographic database files”, import the collected data, choose the type of analysis and counting method, and further set the required parameters. For CiteSpace, create two folders for “Input Directory” and “Output Directory”, set the working path, remove duplicates, create a folder for “Project Home”, set the working path, select a data set, create and name a new project, select the time slicing, set the appropriate parameters, and run the program.

2.5. Comprehensive analysis strategy

For the polynomial fitting curve analysis, we imported the publication number or global citation score and their corresponding years into Excel, added trend lines, further compared the fitting effects of the different fitting functions obtained, and finally determined the objective function based on the correlation coefficient R^2.

For academic elements with different evaluation metrics (such as total publication number, total citation number, average publication number, average citation number, citation number without self-citation, and h-index), we do not consider a single metric but rather a combination of different metrics. Specifically, first, we paid attention to the number of publications and citations, in which we will also compare the average number of publications and citations, and then we evaluated the citation number without self-citation and h-index to finally get the element with the best academic performance. If applicable, we also delved further into potential information, such as the focus of the journal and its derived research spotlight of scholars in this field, the recommendations of the submitting journals, the recent performance of scholars or institutions and the derived follow-up recommendations.

For multi-network visualization analysis of authors, countries, and affiliations, we first divided all elements into several clusters based on the correlation between different elements, after which we further compared the timeline distribution, cooperation heatmap and citation heatmap between different clusters and finally determined the key clusters and nodes.

For multi-network visualization analysis of research hotspots of Nrf2 in cancer, we first divided all the keywords into five clusters according to the correlation between different keywords, after which the keywords of these five clusters were extracted respectively, and then analyzed the specific meanings of the related words based on professional knowledge, and finally outlined the research directions focused by the corresponding clusters. After that, we further compared the timeline distribution, connection density and occurrence density between different clusters and finally determined the key clusters and nodes.

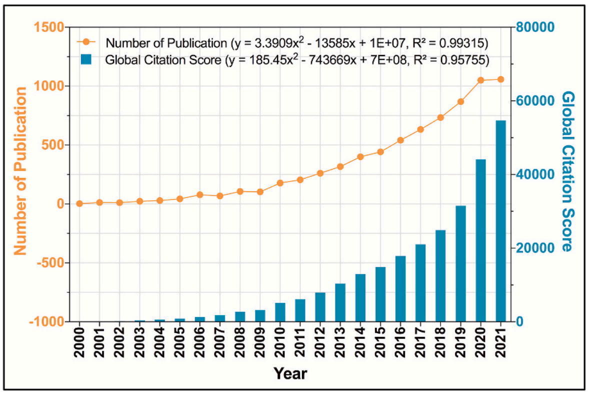


Fig. 1. Timelines and prediction functions of publication number and global citation score about Nrf2 in cancer. The annual publication number (orange) and its corresponding global citation score (blue) were obtained from WOSCC, and then a polynomial fitting curve analysis was performed to establish the prediction functions. R^2 represents the correlation coefficient.

Table 1
The top ten highest cited articles.

Rank	Year	Title	Journal	IF (2021)	Total citation	Type of study
1	2007	Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway	Annual Review of Pharmacology and Toxicology	16.459	2592	Review
2	2012	Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling	Cellular Signalling	4.85	2554	Review
3	2010	The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1	Nature Cell Biology	28.213	1499	Basic Medical Research
4	2011	Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis	Nature	69.504	1415	Basic Medical Research
5	2016	Ferroptosis: process and function	Cell Death and Differentiation	12.067	1309	Review
6	2008	Curcumin: From ancient medicine to current clinical trials	Cellular and Molecular Life Sciences	9.207	1286	Review
7	2008	Regulation of glutathione synthesis	Molecular Aspects of Medicine	16.337	1253	Review
8	2011	Selective autophagy mediated by autophagic adapter proteins	Autophagy	13.391	1215	Review
9	2012	Deconvoluting the context-dependent role for autophagy in cancer	Nature Reviews Cancer	69.8	1187	Review
10	2018	Oncogenic Signaling Pathways in The Cancer Genome Atlas	Cell	66.85	1180	Basic and Clinical Research

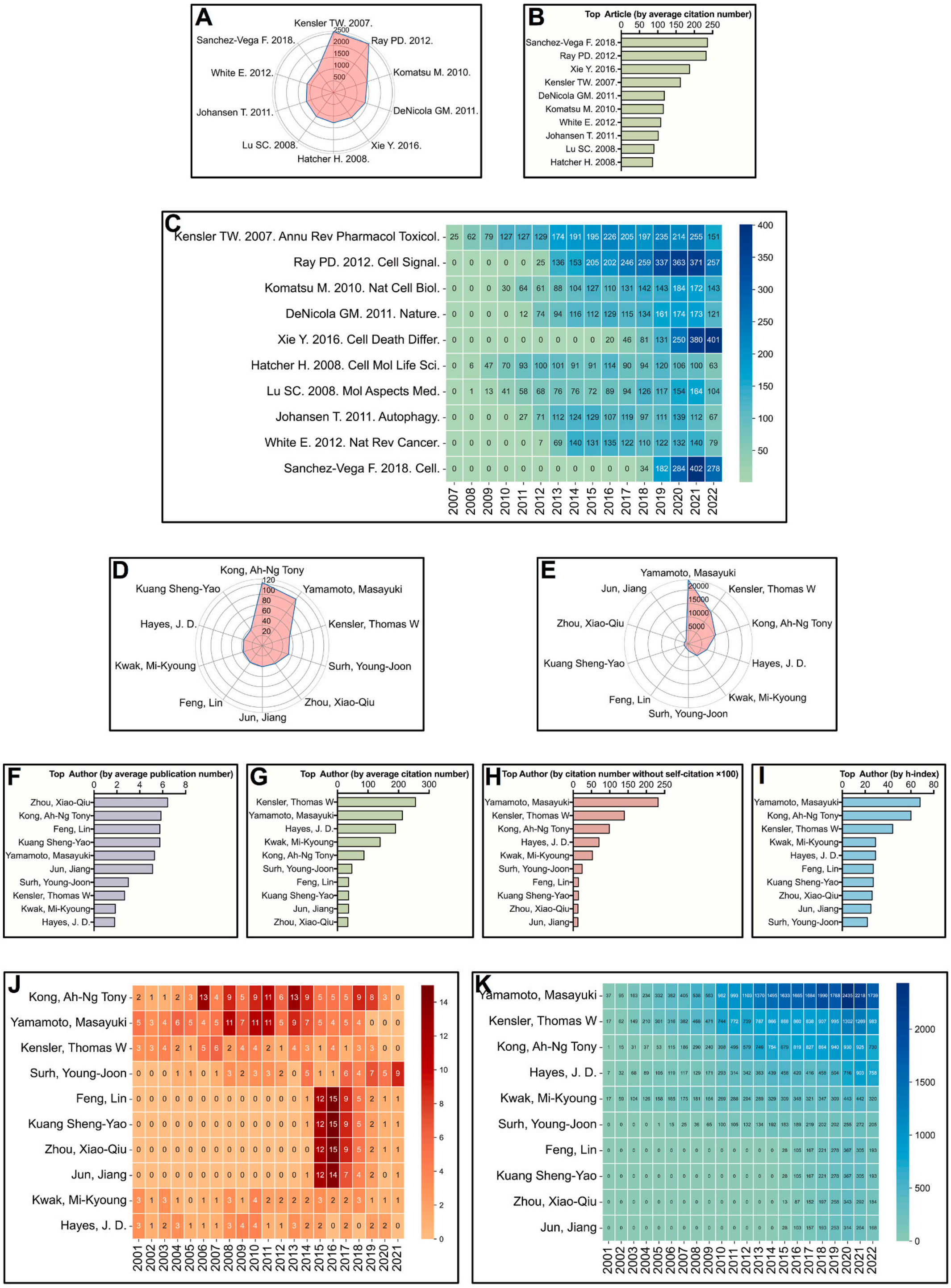
3. Results

3.1. Timelines and prediction functions of publication number and global citation score about Nrf2 in cancer

Fig. 1 displays the annual publication or citation number of the Nrf2 in cancer. The number of annual publications or citations increased year by year and peaked in 2021. The prediction function of the annual number of publications or citations was established by a polynomial fitting curve analysis. The prediction function of the annual publication number is "$y = 3.3909x^2 - 13585x + 1\ E{+}07$" with the correlation coefficient $R^2 = 0.99315$. And the prediction function of the annual number of citations is "$y = 185.45x^2 - 743669x + 7\ E{+}08$" with the correlation coefficient $R^2 = 0.95755$. The solid increments in the publication and citation numbers indicate that this domain has been the center of scholars' attention and is thriving. These results showed that the research on Nrf2 in cancer has begun to get attention and develop rapidly in the past 15 years.

3.2. Scientometrics and visualization analysis of the top ten highest cited articles and top ten most productive authors

The articles in Table 1, whose type mainly is review and publication year is between 2007 and 2013, were ranked in decreasing order of the total citation number. Among these articles, two items published by Kensler TW and Ray PD, respectively, have more than 2500 citations (Fig. 2A). The article with the second-highest total citation also ranks second in the average citation number (Fig. 2B).



(caption on next page)

Fig. 2. Scientometrics and visualization analysis of top ten highest cited articles and top ten most productive authors. (A) Radar chart was used to exhibit the total cited number and rank of the top ten highest cited articles. **(B)** The average citation number of each highest cited article was obtained by the ratio of its total citation number and time from publication to 2022. **(C)** The annual citation number of each highest cited article was visualized by a matrix heatmap. **(D)** The total publication number and rank of the top ten authors with the highest production. **(E)** The total cited number and rank of the top ten authors with the highest production. **(F)** The average publication number of each most productive author was obtained by the ratio of the total publication number and time from publication starting point to 2021. **(G)** The average citation number of each most productive author was obtained by the ratio of the total cited number and time from citation starting point to 2022. **(H)** The total citation number and rank of the top ten authors with the highest production. **(I)** The h-index and rank of the top ten authors with the highest production. **(J, K)** The annual publication or citation number of each highest cited author. Rectangle chart with less light green (C, K) or yellow (J) means less citation number and rectangle chart with more dark blue (C, K) or red (J) means more citation number.

The annual citation number of the top two most cited articles increases year by year (Fig. 2C). The top most cited article published in the Annual Review of Pharmacology and Toxicology (IF = 16.459, Title: Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway, Type of study: Review, 2592 citations). Followed by Cellular Signalling (IF = 4.85, Title: Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling, Type of study: Review, 2554 citations), and Nature Cell Biology (IF = 28.213, Title: The selective autophagy substrate p62 activates the stress-responsive transcription factor Nrf2 through inactivation of Keap1, Type of study: Basic Medical Research, 1499 citations).

Fig. 2D and E shows the top 10 most published and cited authors, respectively, among which Kong Ah-Ng Tony, Yamamoto Masayuki, and Kensler Thomas W are all included in the first three. The top three authors with the most average publication are Zhou Xiao-Qiu, Kong Ah-Ng Tony, and Feng Lin (Fig. 2F). The top three authors with the most average citations are Kensler Thomas W, Yamamoto Masayuki, and Hayes J.D. (Fig. 2G). The top three authors with the most citations without self-citation are Yamamoto Masayuki, Kensler Thomas W, and Kong Ah-Ng Tony (Fig. 2H). The top three authors with the biggest h-index are Yamamoto Masayuki, Kong Ah-Ng Tony, and Kensler Thomas W (Fig. 2I). Fig. 2J and K depict the annual publication and citation number of the top 10 most productive authors, among which Kong Ah-Ng Tony, Yamamoto Masayuki, and Kensler Thomas W are all included in the first three. High-quality articles and outstanding authors in the area of interest will benefit our subsequent research.

3.3. Scientometrics and visualization analysis of the top ten most productive countries or affiliations

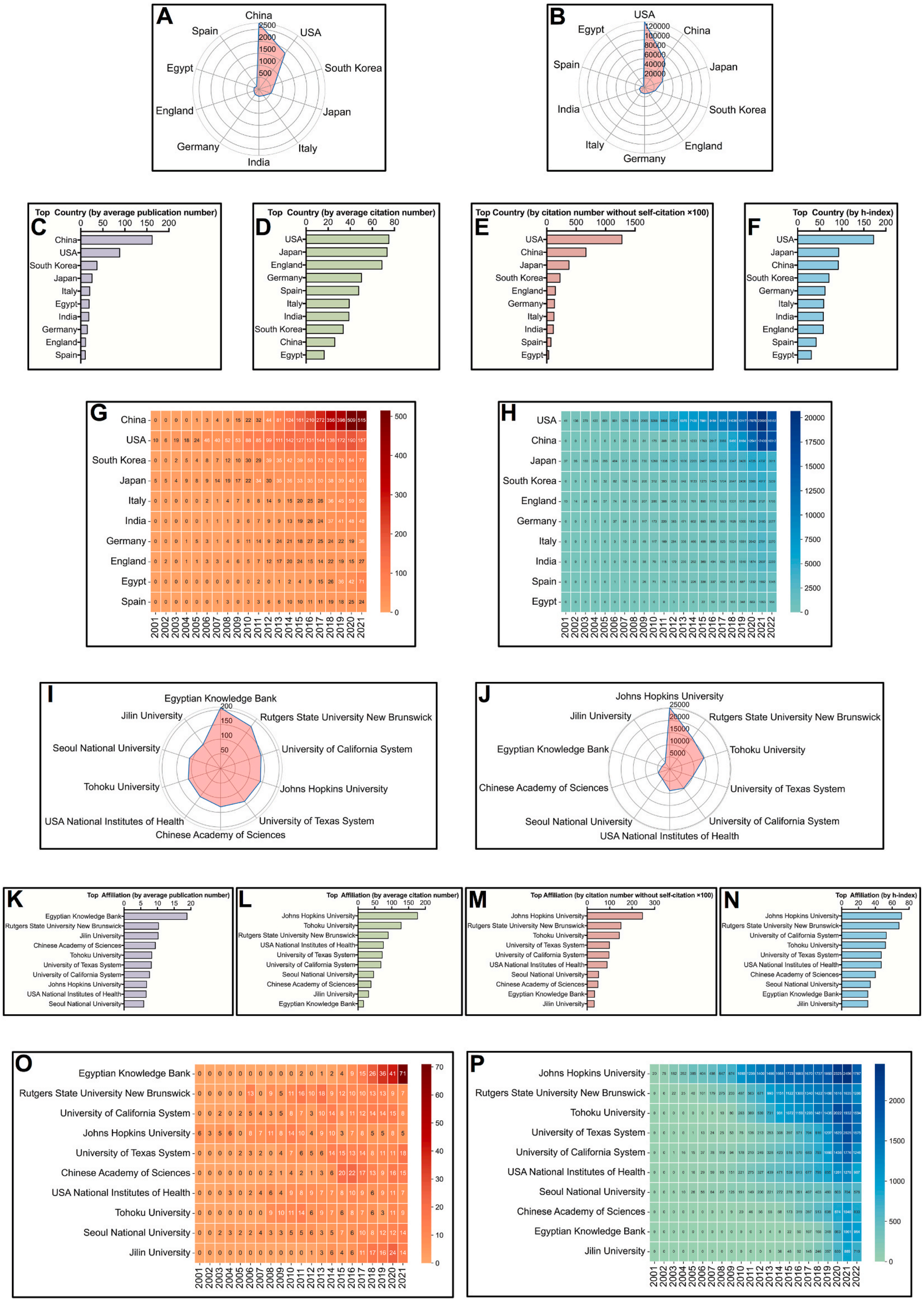
Fig. 3A and B shows the top 10 most published and cited countries, respectively. China possesses the most articles (2756/37.70%), the USA (1854/25.36%), and South Korea (694/9.49%) following. The citations of articles from the USA is 138,278 times, which accounts for 41.15% of the total citations, and is followed by articles from China (71,529/21.29%) and Japan (39,565/11.77%). Furthermore, the USA has the most average citations (74.58), the most citations without self-citation (127,666), and the biggest h-index (172), while China has the most average publication (162.12) (Fig. 3C–F). The number of annual publications in the country with the highest production (China) increases year by year (Fig. 3G). The annual citation number of the top three countries with the highest citation number (USA, China, and Japan) increases year by year (Fig. 3H).

Fig. 3I displays the top ten affiliations with the most Nrf2-related publications in cancer. The affiliation with the highest publication number is the Egyptian Knowledge Bank (207). Rutgers State University New Brunswick (177) is next, followed by the University of California System (145). Fig. 3J displays the top ten affiliations with the most Nrf2-related citations in cancer. The affiliation with the highest citation number is Johns Hopkins University (25,242). Rutgers State University New Brunswick (15,861) is next, followed by Tohoku University (14,820). The top three affiliations with the most average publication are Egyptian Knowledge Bank, Rutgers State University New Brunswick, and Jilin University (Fig. 3K). The top three affiliations with the most average citations are Johns Hopkins University, Tohoku University, and Rutgers State University New Brunswick (Fig. 3L). The top three affiliations with the most citations without self-citation are Johns Hopkins University, Rutgers State University New Brunswick, and Tohoku University (Fig. 3M). The top three affiliations with the biggest h-index are Johns Hopkins University, Rutgers State University New Brunswick, and the University of California System (Fig. 3N). The annual publication number of the top affiliation with the highest production (Egyptian Knowledge Bank) increases year by year (Fig. 3O). The annual citation number of the top two affiliations with the highest citation number (Johns Hopkins University and Rutgers State University New Brunswick) increases year by year (Fig. 3P). Focusing on countries and affiliations with excellent academic performance facilitates our understanding of cutting-edge advances in specific fields.

3.4. Scientometrics and visualization analysis of the top ten most productive research fields or journals

Fig. 4A and B shows the top 10 research fields with the most publications and citations, respectively. The area of Biochemistry Molecular Biology possesses the most articles (1906/23.09%), followed by Pharmacology and Pharmacy (1300/15.75%) and Oncology (1185/14.35%). The citations of articles in the Biochemistry Molecular Biology is 95,755 times, which accounts for 26.25% of the total citations, and is followed by articles in Cell Biology (64,522/17.69%) and Oncology (55,490/15.21%). Furthermore, the area of Biochemistry Molecular Biology has the most average publication (90.62), the most citations without self-citation (89,701), and the biggest h-index (139) (Fig. 4C–E). In contrast, Endocrinology Metabolism has the most average citations (63.94) (Fig. 4F). The annual publication number of the top research field with the highest production (Biochemistry Molecular Biology) increases year by year (Fig. 4G). The annual citation number of the top three countries with the highest citation number (Biochemistry Molecular Biology, Cell Biology and Oncology) increases year by year (Fig. 4H).

Fig. 4I displays the top ten journals with the most Nrf2-related publications in cancer. The journal (Table 2) with the highest



(caption on next page)

Fig. 3. Scientometrics and visualization analysis of top ten most productive countries or affiliations. (A, D) Radar chart was used to exhibit the total publication number and rank of the top ten highest productive countries (A) or affiliations (D). **(B, J)** The total cited number and rank of the top ten most productive countries (B) or affiliations (J). **(C, K)** The average publication number of each most productive country (C) or affiliation (K) was obtained by the ratio of the total publication number and time from publication starting point to 2021. **(D, L)** The average citation number of each most productive country (D) or affiliation (L) was obtained by the ratio of the total cited number and time from citation starting point to 2022. **(E, M)** The total citation number and rank of the top ten most productive country (E) or affiliation (M). **(F, N)** The h-index and rank of the top ten most productive country (F) or affiliation (N). **(G, O)** The annual publication number of each most productive country (G) or affiliation (O) was visualized by a matrix heatmap. **(H, P)** The annual citation number of each most productive country (H) or affiliation (P). Rectangle chart with less light yellow (G, O) or green (H, P) means less citation number and rectangle chart with more dark red (G, O) or blue (H, P) means more citation number.

publication number is Free Radical Biology and Medicine (171). International Journal of Molecular Sciences (141) is next, followed by the Plos One (130). Fig. 4J displays the top ten journals with the most Nrf2-related citations in cancer. The journal (Table 3) with the highest citation number is Free Radical Biology and Medicine (11,466). Plos One (4832) is next, followed by Redox Biology (4688). The top three journals with the most average publication are Antioxidants, Oxidative Medicine and Cellular Longevity, and Redox Biology (Fig. 4K). The top three journals with the most average citations are Free Radical Biology and Medicine, Redox Biology, and Oncotarget (Fig. 4L). The top three journals with the most citations without self-citation are Free Radical Biology and Medicine, Plos One, and Redox Biology (Fig. 4M). The top three journals with the biggest h-index are Free Radical Biology and Medicine, Plos One, and Oncotarget (Fig. 4N). Free Radical Biology and Medicine is the first journal to publish Nrf2-related articles and has maintained a relatively steady publication volume annually (Fig. 4O). The annual citation number of the top three journals with the highest citation number (Free Radical Biology and Medicine, Plos One, and Redox Biology) increases year by year (Fig. 4P). Knowing the journals that are interested in Nrf2 will benefit our submission efforts.

3.5. *Multi-network visualization analysis of authors, countries, and affiliations*

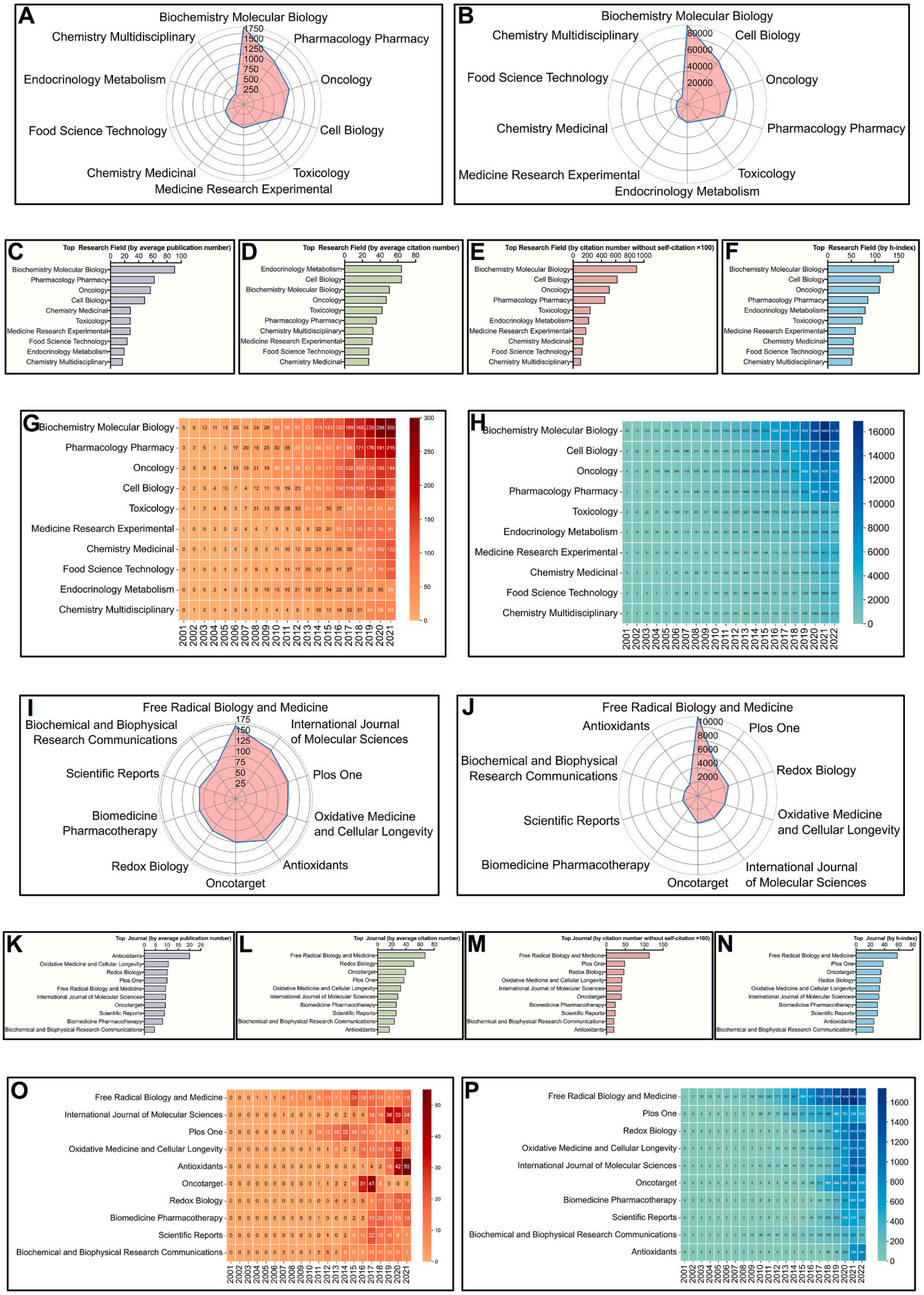
Visualized cluster analysis of cooperation among authors was performed by using VOSviewer (Fig. 5A). Of the 34,653 authors, 906 published at least five documents, and 679 items were chosen for further connection cluster analysis. Six hundred seventy-nine authors were grouped into 31 clusters, and circles framed the first five clusters (Cluster 1: Red; Cluster 2: Green; Cluster 3: Blue; Cluster 4: Yellow; Cluster 5: Purple). Among the five indicated clusters, Hu Rong (Total link strength = 52), Yamamoto Masayuki (Total link strength = 218), Zhang Donna D (Total link strength = 182), Kong Ah-Ng Tony (Total link strength = 255), and Surh Young-Joon (Total link strength = 126) are the critical nodes of the collaboration network. Fig. 5B shows the timeline distribution of the cluster analysis of the author. Cluster 1 is a relatively new collaborative group, while clusters 2 and 4 are relatively early collaborative groups. Fig. 5C shows the cooperation heatmap visualization of an author with other authors. Cluster 4 possesses closer cooperation with other authors than clusters 1, 2, 3, and 5. Fig. 5D shows the citation heatmap visualization of the author. Clusters 2, 3, and 4 have higher citations than clusters 1 and 5.

Visualized cluster analysis of cooperation among countries was performed using VOSviewer (Fig. 5E). Of the 105 countries, 60 published at least five documents, and 103 items were chosen for further connection cluster analysis. One hundred three countries were grouped into 7 clusters, and circles framed the first five clusters (Cluster 1: Red; Cluster 2: Green; Cluster 3: Blue; Cluster 4: Yellow; Cluster 5: Purple). Among the five indicated clusters, Italy (Total link strength = 276), England (Total link strength = 279), Saudi Arabia (Total link strength = 177), India (Total link strength = 161), and the USA (Total link strength = 1049) are the critical nodes of the collaboration network. Fig. 5F shows the timeline distribution of cluster analysis of the country. Cluster 3 is a relatively new collaborative group. Fig. 5G shows the cooperation heatmap visualization of the country with other countries. Cluster 5 possesses closer cooperation with other countries than clusters 1, 2, 3, and 4. Fig. 5H shows the citation heatmap visualization of the country. Cluster 5 has higher citations than clusters 1, 2, 3, and 4.

Visualized cluster analysis of cooperation among affiliations was performed using VOSviewer (Fig. 5I). Of the 5046 affiliations, 701 published at least five documents, and 693 items were chosen for further connection cluster analysis. Six hundred ninety-three affiliations were grouped into 17 clusters, and circles framed the first four clusters (Cluster 1: Red; Cluster 2: Green; Cluster 3: Blue; Cluster 4: Yellow). Among these four clusters, the University of Dundee (Total link strength = 128), Rutgers University (Total link strength = 198), Sun Yat-sen University (Total link strength = 79), and Seoul National University (Total link strength = 120) are the critical nodes of the collaboration network. Fig. 5J shows the timeline distribution of cluster analysis of the affiliation. Cluster 3 is a relatively new collaborative group, while cluster 2 is a relatively early collaborative group. Fig. 5K shows the cooperation heatmap visualization of affiliation with other affiliations. Clusters 1 and 2 possess closer cooperation with other authors than clusters 3 and 4. Fig. 5L shows the citation heatmap visualization of affiliation. Clusters 1 and 2 have higher citations than clusters 3 and 4. Understanding the collaborative relationships between authors, countries, and affiliations will facilitate our research collaborations.

3.6. *Multi-network visualization analysis of research hotspots of Nrf2 in cancer*

Visualized cluster analysis of co-occurrence among author keywords was performed using VOSviewer (Fig. 6A). Of the 10,111 author keywords, 97 keywords appeared at least 26 times, and 97 items were chosen for further occurrence cluster analysis. Ninety-seven author keywords were grouped into 6 clusters, and circles framed the first five clusters (Cluster 1: Red, Cancer Cell Fate Study; Cluster 2: Green, Inflammation and Oxidative Stress Study; Cluster 3: Blue, Cancer Therapy Study; Cluster 4: Yellow, Toxicity Study;



(caption on next page)

Fig. 4. Scientometrics and visualization analysis of top ten most productive research fields or journals. (A, D) Radar chart was used to exhibit the total publication number and rank of the top ten highest productive research fields (A) or journals (D). **(B, J)** The total cited number and rank of the top ten most productive research fields (B) or journals (J). **(C, K)** The average publication number of each most productive research field (C) or journal (K) was obtained by the ratio of the total publication number and time from publication starting point to 2021. **(D, L)** The average citation number of each most productive research field (D) or journal (L) was obtained by the ratio of the total cited number and time from citation starting point to 2022. **(E, M)** The total citation number and rank of the top ten most productive research field (E) or journal (M). **(F, N)** The h-index and rank of the top ten most productive research field (F) or journal (N). **(G, O)** The annual publication number of each most productive research field (G) or journal (O) was visualized by a matrix heatmap. **(H, P)** The annual citation number of each most productive research field (H) or journal (P). Rectangle chart with less light yellow (G, O) or green (H, P) means less citation number and rectangle chart with more dark red (G, O) or blue (H, P) means more citation number.

Table 2
The impact factor of top ten most productive journals.

Journal	Total Publication	IF (2021)	IF (Five Year)
Free Radical Biology and Medicine	171	8.101	8.176
International Journal of Molecular Sciences	141	6.208	6.628
Plos One	130	3.752	4.069
Oxidative Medicine and Cellular Longevity	127	7.31	8.427
Antioxidants	120	7.675	7.886
Oncotarget	102	–	–
Redox Biology	92	10.787	11.271
Biomedicine Pharmacotherapy	89	7.419	6.581
Scientific Reports	89	4.997	5.516
Biochemical and Biophysical Research Communications	85	3.322	3.498

Table 3
The impact factor of top ten highest cited journals.

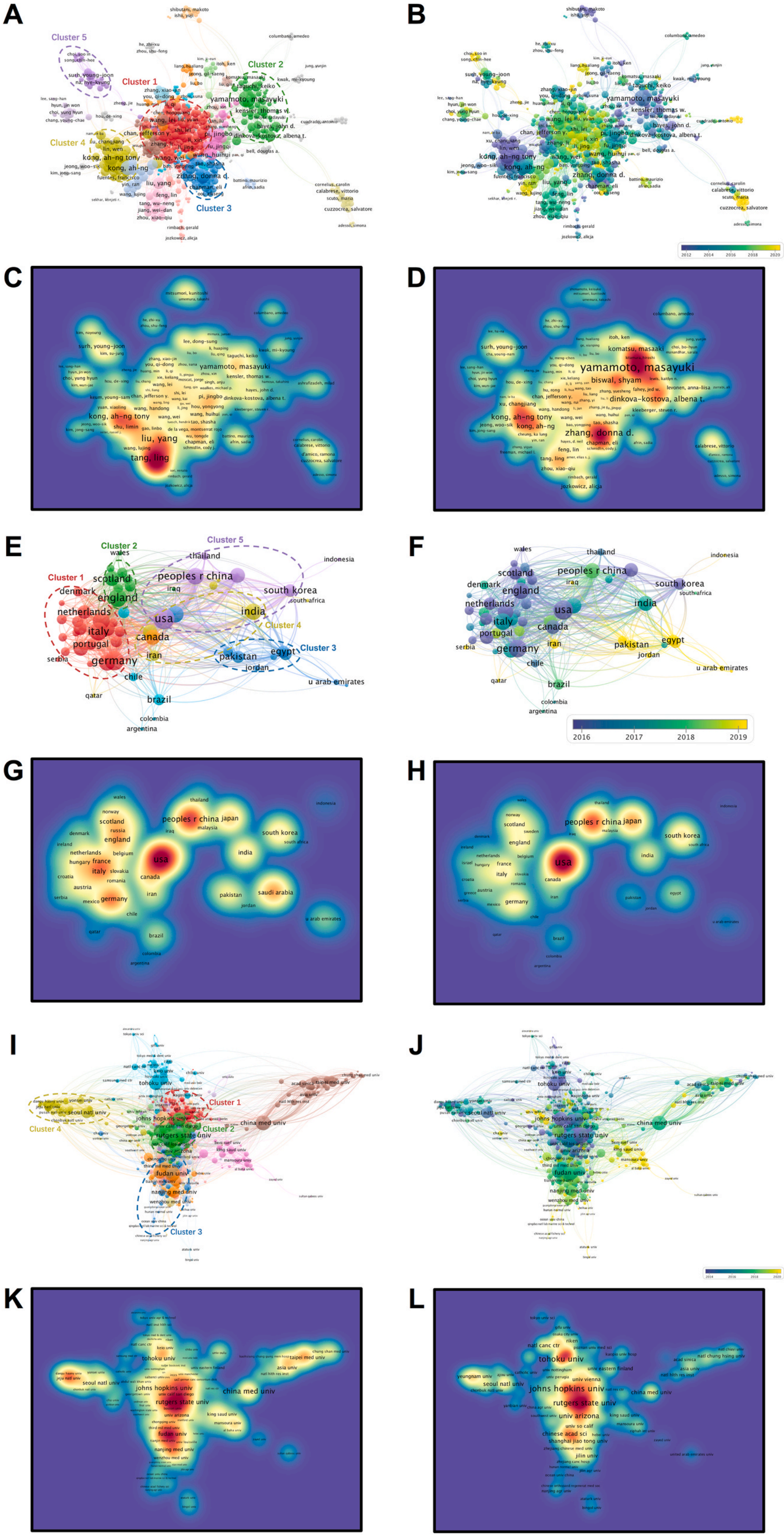
Journal	Total Citation	IF (2021)	IF (Five Year)
Free Radical Biology and Medicine	11,466	8.101	8.176
Plos One	4832	3.752	4.069
Redox Biology	4688	10.787	11.271
Oxidative Medicine and Cellular Longevity	4139	7.31	8.427
International Journal of Molecular Sciences	4025	6.208	6.628
Oncotarget	4016	–	–
Biomedicine Pharmacotherapy	2348	7.419	6.581
Scientific Reports	2317	4.997	5.516
Biochemical and Biophysical Research Communications	1995	3.322	3.498
Antioxidants	1992	7.675	7.886

Cluster 5: Purple, Metabolism Study). Among these five clusters, Nrf2 (Total link strength = 3064), Oxidative Stress (Total link strength = 2045), Sulforaphane (Total link strength = 311), Apoptosis (Total link strength = 920), and Cancer (Total link strength = 481) are the critical nodes of the collaboration network. Fig. 6B shows the timeline distribution of cluster analysis of the author keyword. Clusters 4 and 5 are relatively new collaborative groups, while cluster 3 is a relatively early collaborative group. Fig. 6C shows the connection density visualization of keywords with other keywords. Clusters 1 and 2 connect closely with keywords other than clusters 3, 4, and 5. Fig. 6D shows the occurrence density visualization of the keyword. The keywords "Nrf2″, "Oxidative Stress", "Inflammation", "Apoptosis", and "Keap1″ have higher occurrence density.

CiteSpace was utilized to analyze the top 25 keywords with the strongest citation burst (Fig. 6E). Among the top 25 representatives burst keywords, "antioxidant response element", "gene expression", "antioxidant responsive element", "chemoprevention", "carcinogenesis", "cancer chemoprevention", "free radical", "response element", and "chemopreventive agent" are the terms of cancer therapy study. In addition, the keywords "glutathione s transferase" and "keap1″ are the terms for cancer cell fate study, as well as the keywords "heme oxygenase 1 gene" is the term for inflammation and oxidative stress study. Research hotspots in the field contribute to positioning our research.

3.7. The status and hotspot prediction of research themes of Nrf2 in cancer

R software performed the status analysis and next potential hotspot prediction of research themes of Nrf2 in cancer (Fig. 7). 1700 author's keywords were selected to perform an "InfoMap" cluster algorithm. The "tight junction" and "nrf2″ in quadrant I are the motor themes that are important and well-developed. The "polydatin" and "anti-inflammatory effect" in quadrant II are the niche themes that are well-developed but unimportant to the current research. The "thyroid" and "inflammatory responses" in quadrant III are emerging or declining themes that are poor-developed and Marginal. More interestingly, the thematic map showed that the "immune response" and "intestine" are essential to the field but not well developed, indicating these two themes may be the next



(caption on next page)

Fig. 5. Multi-network visualization analysis of authors, countries and affiliations. (A) Visualized cluster analysis of cooperation among authors. Of the 34,653 authors, 906 published at least five documents, and 679 items were chosen for further connection cluster analysis. **(B)** Timeline distribution of cluster analysis of the author. **(C)** Cooperation heatmap visualization of author with other authors. **(D)** Citation heatmap visualization of author. **(E)** Visualized cluster analysis of cooperation among countries. Of the 105 countries, 60 published at least five documents, and 103 items were chosen for further connection cluster analysis. **(F)** Timeline distribution of cluster analysis of the country. **(G)** Cooperation heatmap visualization of country with other countries. **(H)** Citation heatmap visualization of country. **(I)** Visualized cluster analysis of cooperation among affiliations. Of the 5046 affiliations, 701 published at least five documents, and 693 items were chosen for further connection cluster analysis. **(J)** Timeline distribution of cluster analysis of the affiliation. **(K)** Cooperation heatmap visualization of affiliation with other affiliations. **(L)** Citation heatmap visualization of affiliation. For the visualized cluster analysis, the size of node indicates cooperation strength with other authors. Cluster 1: Red; Cluster 2: Green; Cluster 3: Blue; Cluster 4: Yellow; Cluster 5: Purple. For the timeline distribution of cluster analysis, yellow node comes later than purple node.

research hotspot of Nrf2 in cancer.

4. Discussion

This study is the scientometrics and visualization analysis of oxidative stress modulator Nrf2 in cancer. Using the VOSviewer, CiteSpace, and R packages, numerous Nrf2-related data were extracted, quantified, and visualized from 7168 publications restricted between 2000 and 2021. Through further comprehensive analysis, we revealed the current situations, development textures, and theme hotspots of oxidative stress modulator Nrf2 in cancer and provided some predictions for this domain.

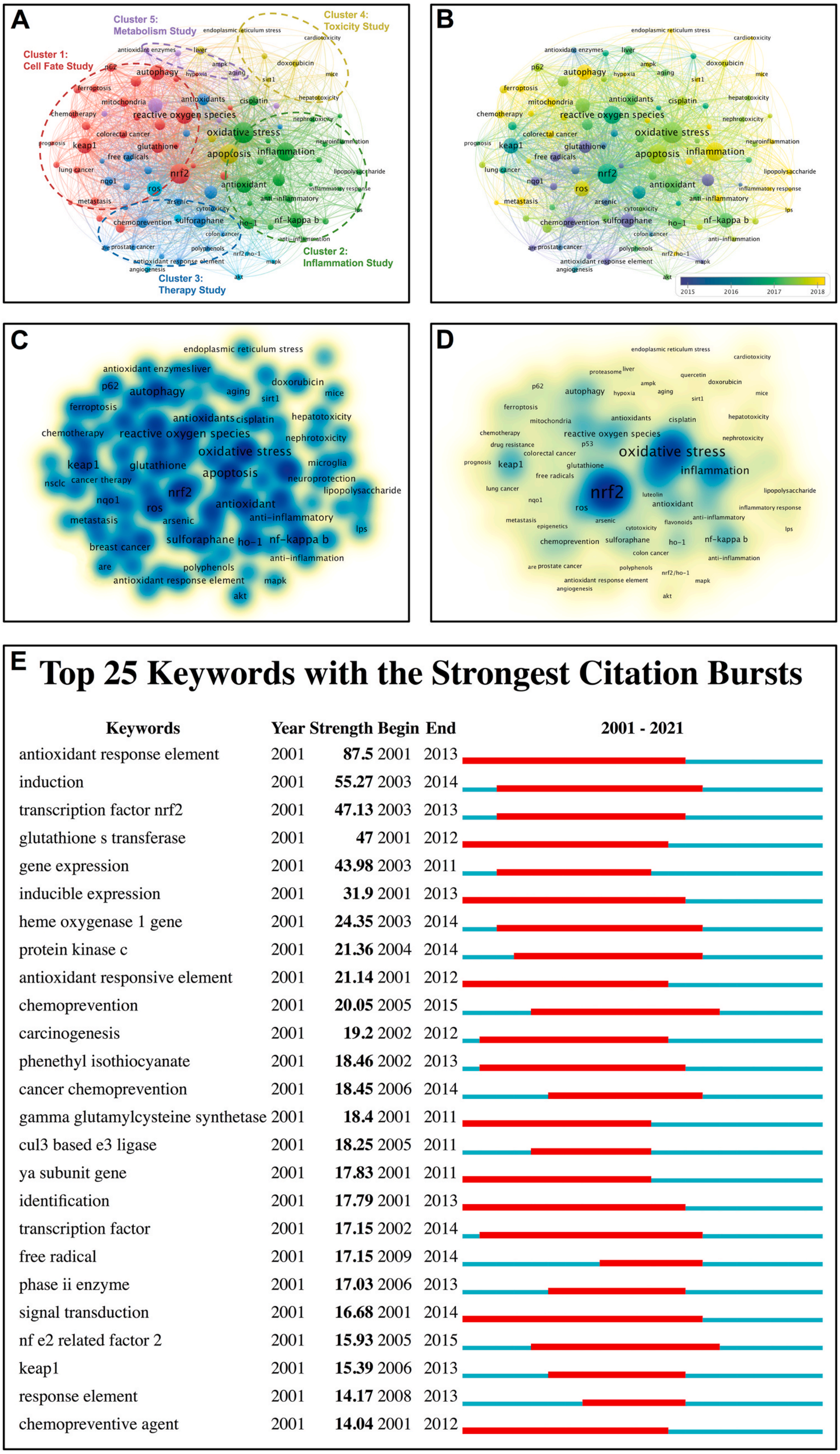
The variation in the publication number is an essential metric for measuring the development trends in a given field [48]. During the last 20 years, publications and citations regarding Nrf2 in cancer have shown a remarkable increasing tendency without too considerable fluctuation. From 2000 to 2007, the number of publications associated with Nrf2 in cancer was small (no more than 100), whereas the publication number has risen steadily since 2008. Moreover, the citation number has grown steadily (more than 10,000) since 2013. Meanwhile, by a polynomial fitting curve analysis, two prediction functions for the annual publication and citation were established (Publication: $y = 3.3909x^2 - 13585x + 1\ E+07$; Citation: $y = 185.45x^2 - 743669x + 7\ E+08$). These results showed that the research on Nrf2 in cancer has begun to get attention and develop rapidly in the past 15 years.

The top most cited article published in the Annual Review of Pharmacology and Toxicology highlighted the critical factors in the adaptive response to counteract acute or chronic cellular damage induced by environmental stress, which may offer a more profound comprehension of Nrf2 in cancer formation and prevention. Meanwhile, the top most cited research article was published in Nature Cell Biology, which aims to publish high-quality papers addressed to cell biology, with a slight leaning towards articles that elucidate the underlying mechanisms of basic cell biology. The publication of Nrf2-related studies in Nature Cell Biology indicates that scholars devote much attention to studying the regulatory mechanism of the transcription factor Nrf2.

Of all the items in scientometrics results about authors, Yamamoto Masayuki (Tohoku University, Japan) and Kensler Thomas W (Fred Hutchinson Cancer Research Center, USA) appear in the top three of most items, proving that both scholars have outstanding academic performance and deserve to be paid close attention to in subsequent studies about Nrf2 in cancer. Simultaneously, the result of visualized cluster analysis of cooperation among authors also demonstrated that Yamamoto Masayuki (Total link strength = 218) is one of the critical nodes of the collaboration network. An Integrated Analysis of results about countries demonstrated that China is the most prolific country, yet the USA is the most influential. Furthermore, the result of visualized cluster analysis of cooperation among countries also demonstrated that USA (Total link strength = 1049) is one of the critical nodes of the collaboration network. Rutgers State University New Brunswick appears in the top three of all the items in scientometrics results about affiliations, proving that it is an institution with comprehensive academic performance. Moreover, the result of visualized cluster analysis of cooperation among affiliations also demonstrated that Rutgers State University New Brunswick (Total link strength = 198) is one of the critical nodes of the collaboration network.

The area of Biochemistry Molecular Biology appears in the top three of all the items in scientometrics results about research fields and even often tops the list, demonstrating that it is a well-developed research field in various dimensions, and Nrf2 in cancer correlates highly with this direction. Free Radical Biology and Medicine appears in most of the top three of the items in scientometrics results about journals and even often tops the list, proving that it is a journal with comprehensive academic performance. To elaborate a little, the journal Free Radical Biology and Medicine (IF = 8.101) mainly spotlights adaptive response mechanisms, redox stress, redox signaling and its transduction, redox compounds, and their mechanisms, metabolism-related diseases and their regulation, antioxidant enzymes and their regulatory networks, and mitochondrial function and related signaling. Furthermore, given its outstanding academic performance and focused scope, this journal may be a good choice for submitting Nrf2-related manuscripts.

The multi-network visualization results of research hotspots indicated that a large part of the present hotspot of studies on Nrf2 in cancer spotlights cancer therapy and its underlying cellular and molecular mechanism. Meanwhile, "Oxidative Stress", "Keap1″, "Apoptosis", and "Cancer" are the intersection of keywords from the multi-network visualization results. Indeed, there is a large number of studies that reported a strong association of Nrf2 with these four terms. Under normal circumstances, Keap1, an endogenous inhibitor of Nrf2, binds to Nrf2 in the cytoplasm and keeps Nrf2 in an inactive state. However, when the cell is under oxidative stress, Nrf2 will release from Keap1 and translocate into the nucleus, in which it combines with the antioxidant response element (ARE), thus regulating oxidative stress-related genes [49–52]. Nowadays, the Keap1-Nrf2-ARE signaling pathway has been deemed a classical signaling pathway in cancer, and targeting Nrf2 has become an essential strategy in cancer therapy [53]. There are many targeted drugs designed to inhibit Nrf2, and one of their essential mechanisms is that inhibition of Nrf2 expression will lead to the accumulation



(caption on next page)

Fig. 6. Multi-network visualization analysis of research hotspots of Nrf2 in cancer. (A) Visualized cluster analysis of co-occurrence among author keywords. Of the 10,111 author keywords, 97 keywords appeared at least 26 times and 97 items were chosen for further occurrence cluster analysis. The size of node indicates occurrence strength with other keywords. Cluster 1 (Red): Cancer Cell Fate Study. Cluster 2 (Green): Inflammation and Oxidative Stress Study. Cluster 3 (Blue): Cancer Therapy Study. Cluster 4 (Yellow): Toxicity Study. Cluster 5 (Purple): Metabolism Study. **(B)** Timeline distribution of the author keywords. Yellow node comes later than purple node. **(C)** Connection density visualization of keyword with other keywords. **(D)** Occurrence density visualization of keyword. **(E)** The top twenty-five keywords with the strongest citation burst. The keywords were ranked by the citation burst strength. The years between the "beginning" and "end" are marked in red, indicating the more influential period for the author keyword. Years to the left of green indicate that the author keyword is still not present, while years to the right indicate that the author keyword is of less influence.

of reactive oxygen radicals in cancer cells, ultimately leading to cancer cell apoptosis [54–56].

Interestingly, the thematic map showed that the "immune response" is essential to the field but not well developed, indicating that the "immune response" may be the next potential research hotspot of Nrf2 in cancer. Recently, some critical studies have also implied this finding. Ahmed et al. demonstrated that Glutathione peroxidase 2, an Nrf2 downstream target gene, is a metabolism-related contributor to the immune checkpoint inhibitor response and the cancer-immune microenvironment [57]. Nishida et al. confirmed that ROS in mitochondria could spark metformin-dependent anti-tumor immunity by activating the Nrf2-mTORC1-p62 signaling axis in tumor-infiltrating CD8T lymphocytes [58]. Hsieh et al. synthesized a new Nrf2 nano-regulator that could induce immune activation in the lung cancer microenvironment [59]. Furthermore, Xu et al. found an association between Nrf2/Keap1 mutations and higher tumor mutation burden or PD-L1 expression, and Nrf2/Keap1 mutations could improve immunotherapy efficacy [60]. Over the past decade, cancer immunotherapy, which eliminates tumor cells by modulating the patient's immune system, has revolutionized the contours of cancer treatment, and we believe this kind of therapy will play an increasingly important role in the future [61–66]. However, the characteristics of Nrf2 in cancer immunotherapy remain imprecise and deserve further exploration.

The present study still has some limitations. First, this study only included the data from the WOSCC, so some critical data in other databases (such as Scopus, and PubMed) may inevitably be missing. Second, due to the incompleteness of the data published in 2022, these data were not included in this study, so some of the results in this paper may change if subsequent studies incorporate complete

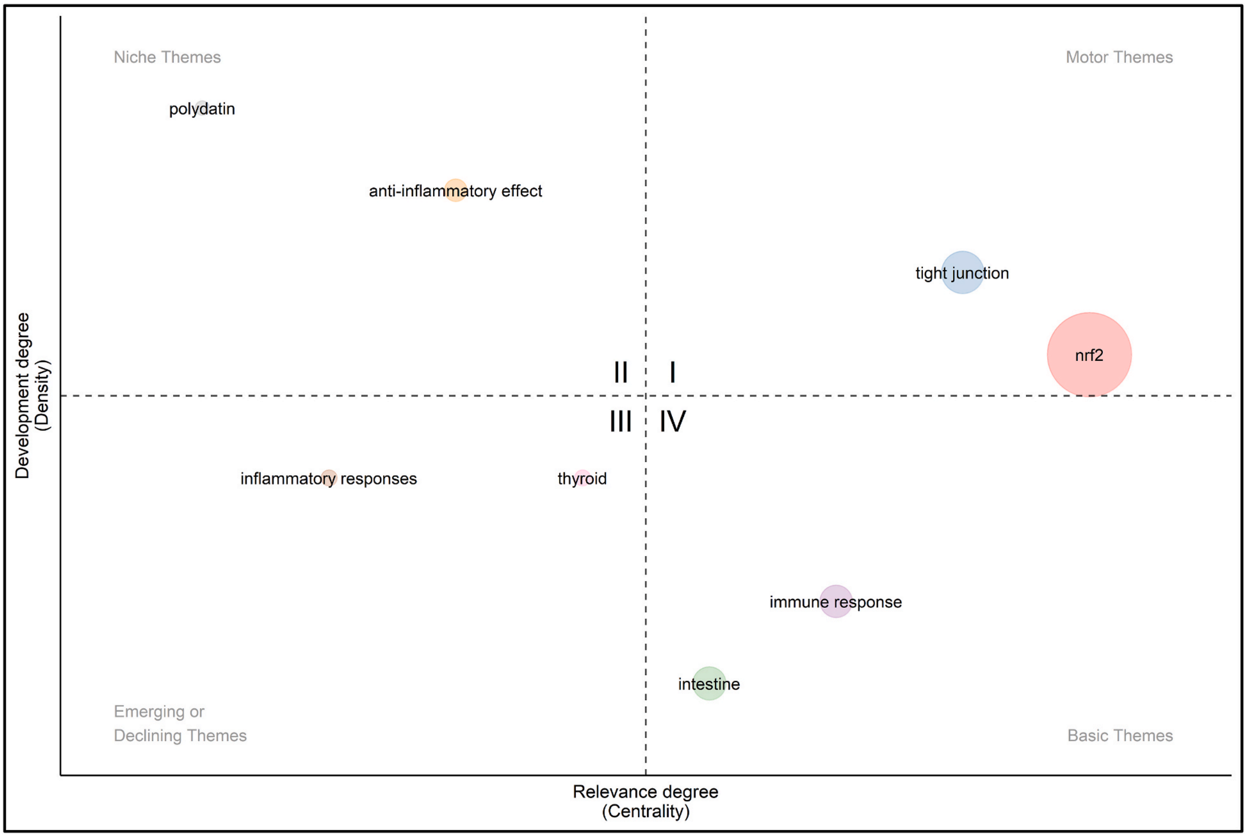


Fig. 7. The status and hotspot prediction of research themes of Nrf2 in cancer. 1700 author's keywords were selected to perform an "InfoMap" cluster algorithm. The x-axis represents the centrality of a specific topic, indicating the level of interactivity with other keywords and reflecting its importance in the field. The y-axis represents topic density, which is considered a metric for the development level. Keywords "immune response" in quadrant IV (Important but under-developed theme).

data from 2022. Third, although the visualization options in this study were conducted from different perspectives (such as overall level, average level, annual level, mixed level, intrinsic level, and extrinsic level), excessive visualization options inevitably led to a semantic load in this study, and further reflection on how to reasonably reduce these options may better hedge the research load. Finally, limited by space, there is still a great deal of potentially important information in this paper, and future research is expected to conduct further exploration.

5. Conclusion

In this study, after scientometric analysis, we found that Biochemistry Molecular Biology correlates with Nrf2 in cancer highly, and Free Radical Biology and Medicine is a good choice for submitting Nrf2-related manuscripts. The current research hotspots of Nrf2 in cancer mainly focus on cancer therapy and its cellular and molecular mechanisms. "antioxidant response element", "gene expression", "antioxidant responsive element", "chemoprevention", "carcinogenesis", "cancer chemoprevention", "free radical", "response element", and "chemopreventive agent" are important for cancer therapy study. In addition, "glutathione s transferase", "keap1″, and "heme oxygenase 1 gene" are important for inflammation and cell fate study. More interestingly, by performing an "InfoMap" algorithm, the thematic map showed that the "immune response" is essential to oxidative stress modulator Nrf2 but not well developed, indicating it deserves further exploration. In conclusion, this scientometric and visual analysis provides a novel perspective on the current situations, development textures, research hotspots, and future directions of oxidative stress modulator Nrf2 in cancer research. Through analyzing massive unstructured data in a stringent manner provided by computer statistics, our work will enable and empower scholars interested in Nrf2 to better understand the global research status and future development directions of this domain.

Author contribution statement

Conceived and designed the experiments: Xiao-Peng Tian, Wei-Juan Huang, and Song-Bin Guo; Performed the experiments: Song-Bin Guo, Sheng Du, Ke-Yu Cai, and Han-Jia Cai; Analyzed and interpreted the data: Song-Bin Guo, Sheng Du, Ke-Yu Cai, and Han-Jia Cai; Contributed reagents, materials, analysis tools or data: Song-Bin Guo, Sheng Du, Ke-Yu Cai, and Han-Jia Cai; Wrote the paper: Song-Bin Guo, Xiao-Peng Tian, and Wei-Juan Huang.

Data availability statement

The dataset of this study can contact corresponding authors with reasonable grounds.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We acknowledge the editors and the reviewers for their constructive comments on this study.

References

[1] C. Tonelli, I.I.C. Chio, D.A. Tuveson, Transcriptional regulation by Nrf2, antioxid, Redox Signal 29 (2018) 1727–1745, https://doi.org/10.1089/ars.2017.7342.
[2] L.-J. Jiang, S.-B. Guo, Z.-Y. Huang, X.-L. Li, X.-H. Jin, W.-J. Huang, X.-P. Tian, PHB promotes bladder cancer cell epithelial-mesenchymal transition via the Wnt/β-catenin signaling pathway, Pathol. Res. Pract. 247 (2023), 154536, https://doi.org/10.1016/j.prp.2023.154536.
[3] N. Li, Y. Zhang, J. Lv, D. Sun, J. Lin, Q. Pang, H. Li, Z. Cao, Y. Liu, Z. Li, X. Fang, D. Li, H. Bai, Y. An, J. Jiang, R. Zhang, Q. Yang, Protective effects of ginsenoside CK against oxidative stress-induced neuronal damage, assessed with 1H-NMR-based metabolomics, Acta Mater. Medica 1 (2022), https://doi.org/10.15212/AMM-2022-0009.
[4] W.-J. Huang, S.-B. Guo, H. Shi, X.-L. Li, Y. Zhu, M. Li, L.-Y. Song, R.-M. Yu, Q.-Q. Cai, X.-P. Tian, The β-catenin-LINC00183-miR-371b-5p-Smad2/LEF1 axis promotes adult T-cell lymphoblastic lymphoma progression and chemoresistance, J. Exp. Clin. Cancer Res. 42 (2023) 105, https://doi.org/10.1186/s13046-023-02670-9.
[5] Y. Guo, B. Hu, B. Fu, H. Zhu, Atovaquone at clinically relevant concentration overcomes chemoresistance in ovarian cancer via inhibiting mitochondrial respiration, Pathol. Res. Pract. 224 (2021), 153529, https://doi.org/10.1016/j.prp.2021.153529.
[6] K. Smolková, E. Mikó, T. Kovács, A. Leguina-Ruzzi, A. Sipos, P. Bai, Nuclear factor erythroid 2-related factor 2 in regulating cancer metabolism, antioxid, Redox Signal 33 (2020) 966–997, https://doi.org/10.1089/ars.2020.8024.
[7] C.-H. Chang, S. Pauklin, Ros, Tgfβ, From pancreatic tumour growth to metastasis, J. Exp. Clin. Cancer Res. 40 (2021) 152, https://doi.org/10.1186/s13046-021-01960-4.
[8] R.I. Mancuso, M.A. Foglio, S.T. Olalla Saad, Artemisinin-type drugs for the treatment of hematological malignancies, Cancer Chemother. Pharmacol. 87 (2021) 1–22, https://doi.org/10.1007/s00280-020-04170-5.
[9] R. Kohan, A. Collin, S. Guizzardi, N. Tolosa de Talamoni, G. Picotto, Reactive oxygen species in cancer: a paradox between pro- and anti-tumour activities, Cancer Chemother. Pharmacol. 86 (2020) 1–13, https://doi.org/10.1007/s00280-020-04103-2.
[10] B. Zhang, C. Pan, C. Feng, C. Yan, Y. Yu, Z. Chen, C. Guo, X. Wang, Role of mitochondrial reactive oxygen species in homeostasis regulation, Redox Rep. 27 (2022) 45–52, https://doi.org/10.1080/13510002.2022.2046423.
[11] M. Liu, Q. Yan, B. Peng, Y. Cai, S. Zeng, Z. Xu, Y. Yan, Z. Gong, Use of cucurbitacins for lung cancer research and therapy, Cancer Chemother. Pharmacol. 88 (2021) 1–14, https://doi.org/10.1007/s00280-021-04265-7.

[12] J.-J. Qin, X.-D. Cheng, J. Zhang, W.-D. Zhang, Dual roles and therapeutic potential of Keap1-Nrf2 pathway in pancreatic cancer: a systematic review, Cell Commun. Signal. 17 (2019) 121, https://doi.org/10.1186/s12964-019-0435-2.
[13] K. Iida, K. Itoh, Y. Kumagai, R. Oyasu, K. Hattori, K. Kawai, T. Shimazui, H. Akaza, M. Yamamoto, Nrf2 is essential for the chemopreventive efficacy of Oltipraz against urinary, Bladder Carcinogenesis, Cancer Res. 64 (2004) 6424–6431, https://doi.org/10.1158/0008-5472.CAN-04-1906.
[14] M. Russo, C. Spagnuolo, G.L. Russo, K. Skalicka-Woźniak, M. Daglia, E. Sobarzo-Sánchez, S.F. Nabavi, S.M. Nabavi, Nrf2 targeting by sulforaphane: a potential therapy for cancer treatment, Crit. Rev. Food Sci. Nutr. 58 (2018) 1391–1405, https://doi.org/10.1080/10408398.2016.1259983.
[15] W. Weng, A. Goel, Curcumin and colorectal cancer: an update and current perspective on this natural medicine, Semin. Cancer Biol. 80 (2022) 73–86, https://doi.org/10.1016/j.semcancer.2020.02.011.
[16] A. Garufi, S. Baldari, R. Pettinari, M.S. Gilardini Montani, V. D'Orazi, G. Pistritto, A. Crispini, E. Giorno, G. Toietta, F. Marchetti, M. Cirone, G. D'Orazi, A ruthenium(II)-curcumin compound modulates NRF2 expression balancing the cancer cell death/survival outcome according to p53 status, J. Exp. Clin. Cancer Res. 39 (2020) 122, https://doi.org/10.1186/s13046-020-01628-5.
[17] B. Ren, M.X.-Y. Kwah, C. Liu, Z. Ma, M.K. Shanmugam, L. Ding, X. Xiang, P.C.-L. Ho, L. Wang, P.S. Ong, B.C. Goh, Resveratrol for cancer therapy: challenges and future perspectives, Cancer Lett. 515 (2021) 63–72, https://doi.org/10.1016/j.canlet.2021.05.001.
[18] W. Sun, H. Li, Y. Shen, H. Xiao, Resveratrol attenuates rotenone-induced inflammation and oxidative stress via STAT1 and Nrf2/Keap1/SLC7A11 pathway in a microglia cell line, Pathol. Res. Pract. 225 (2021), 153576, https://doi.org/10.1016/j.prp.2021.153576.
[19] J.M. DeBlasi, A. Falzone, S. Caldwell, N. Prieto-Farigua, J.R. Prigge, E.E. Schmidt, I.I.C. Chio, F.A. Karreth, G.M. DeNicola, Distinct Nrf2 Signaling Thresholds Mediate Lung Tumor Initiation and Progression, Cancer Res., 2023, https://doi.org/10.1158/0008-5472.CAN-22-3848. CAN-22-3848.
[20] C. Wang, T. Cheng, Q. Lu, W. Li, B. Liu, L. Yue, M. Du, W. Sheng, Z. Lu, J. Yang, F. Geng, X. Gao, J. Lü, X. Pan, Oxygen therapy accelerates apoptosis induced by selenium compounds via regulating Nrf2/MAPK signaling pathway in hepatocellular carcinoma, Pharmacol. Res. 187 (2023), 106624, https://doi.org/10.1016/j.phrs.2022.106624.
[21] H. Kahroba, M. Shirmohamadi, M.S. Hejazi, N. Samadi, The Role of Nrf2 signaling in cancer stem cells: from stemness and self-renewal to tumorigenesis and chemoresistance, Life Sci. 239 (2019), 116986, https://doi.org/10.1016/j.lfs.2019.116986.
[22] X. Wang, T. Zhou, X. Yang, X. Cao, G. Jin, P. Zhang, J. Guo, K. Rong, B. Li, Y. Hu, K. Liu, P. Ma, A. Qin, J. Zhao, DDRGK1 enhances osteosarcoma chemoresistance via inhibiting KEAP1-mediated NRF2 ubiquitination, Adv. Sci. (2023), 2204438, https://doi.org/10.1002/advs.202204438.
[23] Y. Jeong, N.T. Hoang, A. Lovejoy, H. Stehr, A.M. Newman, A.J. Gentles, W. Kong, D. Truong, S. Martin, A. Chaudhuri, D. Heiser, L. Zhou, C. Say, J.N. Carter, S. M. Hiniker, B.W. Loo, R.B. West, P. Beachy, A.A. Alizadeh, M. Diehn, Role of *KEAP1/NRF2* and *TP53* mutations in lung squamous cell carcinoma development and radiation resistance, Cancer Discov. 7 (2017) 86–101, https://doi.org/10.1158/2159-8290.CD-16-0127.
[24] M. Rojo de la Vega, E. Chapman, D.D. Zhang, NRF2 and the hallmarks of cancer, Cancer Cell 34 (2018) 21–43, https://doi.org/10.1016/j.ccell.2018.03.022.
[25] H. Zeng, X. Zhao, C. Tang, Downregulation of SELENBP1 enhances oral squamous cell carcinoma chemoresistance through KEAP1–NRF2 signaling, Cancer Chemother. Pharmacol. 88 (2021) 223–233, https://doi.org/10.1007/s00280-021-04284-4.
[26] K.-J. Tsai, H.-Y. Tsai, C.-C. Tsai, T.-Y. Chen, T.-H. Hsieh, C.-L. Chen, L. Mbuyisa, Y.-B. Huang, M.-W. Lin, Luteolin inhibits breast cancer stemness and enhances chemosensitivity through the nrf2-mediated pathway, Molecules 26 (2021) 6452, https://doi.org/10.3390/molecules26216452.
[27] X.J. Wang, J.D. Hayes, C.J. Henderson, C.R. Wolf, Identification of retinoic acid as an inhibitor of transcription factor Nrf2 through activation of retinoic acid receptor alpha, Proc. Natl. Acad. Sci. USA 104 (2007) 19589–19594, https://doi.org/10.1073/pnas.0709483104.
[28] L. Ji, N. Moghal, X. Zou, Y. Fang, S. Hu, Y. Wang, M.S. Tsao, The NRF2 Antagonist ML385 Inhibits PI3K-mTOR Signaling and Growth of Lung Squamous Cell Carcinoma Cells, Cancer Med, 2022, https://doi.org/10.1002/cam4.5311 cam4.5311.
[29] A. Arlt, S. Sebens, S. Krebs, C. Geismann, M. Grossmann, M.-L. Kruse, S. Schreiber, H. Schäfer, Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity, Oncogene 32 (2013) 4825–4835, https://doi.org/10.1038/onc.2012.493.
[30] S. Guo, J. Zhang, C. Wei, Z. Lu, R. Cai, D. Pan, H. Zhang, B. Liang, Z. Zhang, Anticancer effects of brusatol in nasopharyngeal carcinoma through suppression of the Akt/mTOR signaling pathway, Cancer Chemother. Pharmacol. 85 (2020) 1097–1108, https://doi.org/10.1007/s00280-020-04083-3.
[31] S.J. Cai, Y. Liu, S. Han, C. Yang, Brusatol, an NRF2 inhibitor for future cancer therapeutic, Cell Biosci. 9 (2019) 45, https://doi.org/10.1186/s13578-019-0309-8.
[32] G. Tossetta, D. Marzioni, Natural and synthetic compounds in Ovarian Cancer: a focus on NRF2/KEAP1 pathway, Pharmacol. Res. 183 (2022), 106365, https://doi.org/10.1016/j.phrs.2022.106365.
[33] H. Li, W. Wei, H. Xu, Drug discovery is an eternal challenge for the biomedical sciences, Acta Mater. Medica 1 (2022), https://doi.org/10.15212/AMM-2022-1001.
[34] J. Mingers, L. Leydesdorff, A review of theory and practice in scientometrics, Eur. J. Oper. Res. 246 (2015) 1–19, https://doi.org/10.1016/j.ejor.2015.04.002.
[35] A. Martín-Martín, M. Thelwall, E. Orduna-Malea, E. Delgado López-Cózar, Google Scholar, Microsoft academic, Scopus, dimensions, web of science, and OpenCitations' COCI: a multidisciplinary comparison of coverage via citations, Scientometrics 126 (2021) 871–906, https://doi.org/10.1007/s11192-020-03690-4.
[36] B. Tran, G. Vu, G. Ha, Q.-H. Vuong, M.-T. Ho, T.-T. Vuong, V.-P. La, M.-T. Ho, K.-C. Nghiem, H. Nguyen, C. Latkin, W. Tam, N.-M. Cheung, H.-K. Nguyen, C. Ho, R. Ho, Global evolution of research in artificial intelligence in health and medicine: a bibliometric study, J. Clin. Med. 8 (2019) 360, https://doi.org/10.3390/jcm8030360.
[37] H. Zhao, J.-B. Liu, Z.-F. Bao, Y.-X. Xu, Z.-Q. Wang, Global research trends in dental stem cells: a bibliometric and visualized study, Tissue Eng. B Rev. 28 (2022) 733–744, https://doi.org/10.1089/ten.teb.2021.0080.
[38] J. Jiang, W. Lyu, N. Chen, A bibliometric analysis of diffuse large B-cell lymphoma research from 2001 to 2020, Comput, Biol. Med. 146 (2022), 105565, https://doi.org/10.1016/j.compbiomed.2022.105565.
[39] G. Adunlin, V. Diaby, H. Xiao, Application of multicriteria decision analysis in health care: a systematic review and bibliometric analysis, Health Expect. 18 (2015) 1894, https://doi.org/10.1111/hex.12287. –1905.
[40] J. Zhao, Z. Han, Y. Ma, H. Liu, T. Yang, Research progress in digital pathology: a bibliometric and visual analysis based on Web of Science, Pathol. Res. Pract. 240 (2022), 154171, https://doi.org/10.1016/j.prp.2022.154171.
[41] J. Fu, Z. Jiang, Y. Hong, S. Liu, D. Kong, Z. Zhong, Y. Luo, Global scientific research on social participation of older people from 2000 to 2019: a bibliometric analysis, Int. J. Older People Nurs. 16 (2021), https://doi.org/10.1111/opn.12349.
[42] D. Xu, Y.-L. Wang, K.-T. Wang, Y. Wang, X.-R. Dong, J. Tang, Y.-L. Cui, A scientometrics analysis and visualization of depressive disorder, Curr. Neuropharmacol. 19 (2021) 766–786, https://doi.org/10.2174/1570159X18666200905151333.
[43] M. Liang, Y. Meng, S. Zhou, Z. Tao, L. Tao, Research hotspots and trends analysis of ankylosing spondylitis: a bibliometric and scientometric analysis from 2009 to 2018, Ann. Transl. Med. 8 (2020), https://doi.org/10.21037/atm-20-1259, 1445–1445.
[44] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2010) 523–538, https://doi.org/10.1007/s11192-009-0146-3.
[45] N.J. van Eck, L. Waltman, Citation-based clustering of publications using CitNetExplorer and VOSviewer, Scientometrics 111 (2017) 1053–1070, https://doi.org/10.1007/s11192-017-2300-7.
[46] C. Chen, M. Song, Visualizing a field of research: a methodology of systematic scientometric reviews, PLoS One 14 (2019), e0223994, https://doi.org/10.1371/journal.pone.0223994.
[47] C. Chen, A glimpse of the first eight months of the COVID-19 literature on Microsoft academic graph: themes, citation contexts, and uncertainties, Front. Res. Metr. Anal. 5 (2020), 607286, https://doi.org/10.3389/frma.2020.607286.
[48] K. Cheng, Q. Guo, Z. Shen, W. Yang, Y. Wang, Z. Sun, H. Wu, Bibliometric analysis of global research on cancer photodynamic therapy: focus on nano-related research, Front. Pharmacol. 13 (2022), 927219, https://doi.org/10.3389/fphar.2022.927219.
[49] J.D. Hayes, A.T. Dinkova-Kostova, K.D. Tew, Oxidative stress in cancer, Cancer Cell 38 (2020) 167–197, https://doi.org/10.1016/j.ccell.2020.06.001.

[50] A. Cuadrado, A.I. Rojo, G. Wells, J.D. Hayes, S.P. Cousin, W.L. Rumsey, O.C. Attucks, S. Franklin, A.-L. Levonen, T.W. Kensler, A.T. Dinkova-Kostova, Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases, Nat. Rev. Drug Discov. 18 (2019) 295–317, https://doi.org/10.1038/s41573-018-0008-x.

[51] S. Jia, Q. Chen, J. Wu, X. Yao, J. Shao, X. Cheng, C. Zhang, D. Cen, Y. Wang, Z. Shen, L. Shan, X. Yao, Danshensu derivative ADTM ameliorates CCl4-induced acute liver injury in mice through inhibiting oxidative stress and apoptosis, Pathol. Res. Pract. 228 (2021), 153656, https://doi.org/10.1016/j.prp.2021.153656.

[52] A. Raghunath, K. Sundarraj, R. Nagarajan, F. Arfuso, J. Bian, A.P. Kumar, G. Sethi, E. Perumal, Antioxidant response elements: discovery, classes, regulation and potential applications, Redox Biol. 17 (2018) 297–314, https://doi.org/10.1016/j.redox.2018.05.002.

[53] F. Li, I.A.M. Aljahdali, R. Zhang, K.L. Nastiuk, J.J. Krolewski, X. Ling, Kidney cancer biomarkers and targets for therapeutics: survivin (BIRC5), XIAP, MCL-1, HIF1α, HIF2α, NRF2, MDM2, MDM4, p53, KRAS and AKT in renal cell carcinoma, J. Exp. Clin. Cancer Res. 40 (2021) 254, https://doi.org/10.1186/s13046-021-02026-1.

[54] D.D. Zhang, E. Chapman, The role of natural products in revealing NRF2 function, Nat. Prod. Rep. 37 (2020) 797–826, https://doi.org/10.1039/C9NP00061E.

[55] S.-B. Guo, W.-J. Huang, X.-P. Tian, Brusatol modulates diverse cancer hallmarks and signaling pathways as a potential cancer therapeutic, Acta Mater. Medica 1 (2022), https://doi.org/10.15212/AMM-2022-0014.

[56] E. Crisman, P. Duarte, E. Dauden, A. Cuadrado, M.I. Rodríguez-Franco, M.G. López, R. León, KEAP1-NRF2 protein–protein interaction inhibitors: design, pharmacological properties and therapeutic potential, Med. Res. Rev. 43 (2023) 237–287, https://doi.org/10.1002/med.21925.

[57] K.M. Ahmed, R. Veeramachaneni, D. Deng, N. Putluri, V. Putluri, M.F. Cardenas, D.A. Wheeler, W.K. Decker, A.I. Frederick, S. Kazi, A.G. Sikora, V. C. Sandulache, M.J. Frederick, Glutathione peroxidase 2 is a metabolic driver of the tumor immune microenvironment and immune checkpoint inhibitor response, J. Immunother. Cancer. 10 (2022), e004752, https://doi.org/10.1136/jitc-2022-004752.

[58] M. Nishida, N. Yamashita, T. Ogawa, K. Koseki, E. Warabi, T. Ohue, M. Komatsu, H. Matsushita, K. Kakimi, E. Kawakami, K. Shiroguchi, H. Udono, Mitochondrial reactive oxygen species trigger metformin-dependent antitumor immunity via activation of Nrf2/mTORC1/p62 axis in tumor-infiltrating CD8T lymphocytes, J. Immunother. Cancer. 9 (2021), e002954, https://doi.org/10.1136/jitc-2021-002954.

[59] C.-H. Hsieh, H.-C. Hsieh, F.-H. Shih, P.-W. Wang, L.-X. Yang, D.-B. Shieh, Y.-C. Wang, An innovative NRF2 nano-modulator induces lung cancer ferroptosis and elicits an immunostimulatory tumor microenvironment, Theranostics 11 (2021) 7072–7091, https://doi.org/10.7150/thno.57803.

[60] X. Xu, Y. Yang, X. Liu, N. Cao, P. Zhang, S. Zhao, D. Chen, L. Li, Y. He, X. Dong, K. Wang, H. Lin, N. Mao, L. Liu, *NFE2L2/KEAP1* mutations correlate with higher tumor mutational burden value/PD-L1 expression and potentiate improved clinical outcome with immunotherapy, Oncol. 25 (2020), https://doi.org/10.1634/theoncologist.2019-0885 e955–e963.

[61] R. Offringa, L. Kötzner, B. Huck, K. Urbahns, The expanding role for small molecules in immuno-oncology, Nat. Rev. Drug Discov. 21 (2022) 821–840, https://doi.org/10.1038/s41573-022-00538-9.

[62] S. Mehdizadeh, H. Bayatipoor, S. Pashangzadeh, R. Jafarpour, Z. Shojaei, M. Motallebnezhad, Immune checkpoints and cancer development: therapeutic implications and future directions, Pathol. Res. Pract. 223 (2021), 153485, https://doi.org/10.1016/j.prp.2021.153485.

[63] U. Mehraj, A.H. Dar, N.A. Wani, M.A. Mir, Tumor microenvironment promotes breast cancer chemoresistance, Cancer Chemother. Pharmacol. 87 (2021) 147–158, https://doi.org/10.1007/s00280-020-04222-w.

[64] J. Xie, L. Fu, L. Jin, Immunotherapy of gastric cancer: past, future perspective and challenges, Pathol. Res. Pract. 218 (2021), 153322, https://doi.org/10.1016/j.prp.2020.153322.

[65] C.-K. Shan, Y.-B. Du, X.-T. Zhai, Y.-X. Wang, Y. Li, J.-H. Gong, Z.-J. Ge, X.-J. Liu, Y.-S. Zhen, Pingyangmycin enhances the antitumor efficacy of anti-PD-1 therapy associated with tumor-infiltrating CD8+ T cell augmentation, Cancer Chemother, Pharmacol 87 (2021) 425–436, https://doi.org/10.1007/s00280-020-04209-7.

[66] X. Xu, R. Li, R. Dong, Y. Yang, H. Wang, J. Cheng, Y. Liu, J. Ye, In vitro characterization and cellular uptake profiles of TAMs-targeted lipid calcium carbonate nanoparticles for cancer immunotherapy, Acta Mater. Medica 1 (2022), https://doi.org/10.15212/AMM-2022-0030.