Araştırma Makalesi/Original Article

T.C SAĞLIK BAKANLIĞI
Sağlık Hizmetleri Genel Müdürlüğü
GETAT Daire Başkanlığı

Anadolu Tıbbı Dergisi

ISSN: 2822-3373 https:// anadolutibbidergisi.saglik.gov.tr Yıl/Year: 2023 Eylül/September Cilt/Volume:2 Sayı/Issue:2 Bakanlık Yayın No:1230

CHINESE MEDICINE FOR PULMONARY FIBROSIS: A BIBLIOMETRIC REVIEW FROM 2005 TO 2023

Xiaodi LV[1,2]
Bin WANG[3]
Zhen GAO[1,2]
Weifeng TANG[1,2]
Jingcheng DONG[1,2]
Ying WEI[1,2]

ABSTRACT

To enhance our comprehension of the progression in the field of Chinese medicine for pulmonary fibrosis (PF), to grasp the fundamental shift in the understanding of role of Chinese medicine in PF management, to delve into potential and efficacious pharmacological mechanisms for PF, and to uncover innovative diagnostic targets, we employed a bibliometric analysis to examine articles pertaining to Chinese medicine for PF published between 2005 and 2023. Drawing upon information derived from the Web of Science Core Collection spanning the years 2005 to 2023, a thorough compilation of 389 articles focused on Chinese medicine for PF has been identified, distributed across an array of 389 scholarly journals. These contributions were authored by 2334 individuals associated with 395 organizations representing diverse regions, encompassing 16 distinct countries or territories. Our findings shed light on the evolution of traditional Chinese medicine's application and research in effective PF therapy, the evolving paradigm guiding this domain, the exploration and integration of novel mechanisms, and the emerging frontiers within this realm.

Keywords: pulmonary fibrosis, Chinese medicine, targets, bibliometric analysis, therapy.

1.INTRODUCTION

Pulmonary fibrosis (PF) plays a notable role in the worldwide burden of illness and death. Pinpointing the precise frequency and prevalence of this ailment presents a formidable challenge. Meanwhile, pulmonary fibrosis emerges as the advanced stage of various interstitial lung ailments, encompassing the idiopathic interstitial pneumonias. PF is a persistent and gradually progressing interstitial lung disorder originating from diverse underlying factors. It is characterized by the accumulation of inflammatory cells such as macrophages, neutrophils, and lymphocytes within the alveoli. This is accompanied by the multiplication and conversion of fibroblasts, leading to an excessive deposition of extracellular matrix (ECM) within the pulmonary interstitial space. Ultimately, this cascade of events instigates noteworthy modifications in the structure of the inherent lung tissue (1, 2). Within the realm of idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) takes the forefront as the most prevalent and deadly condition, boasting a median survival of 3–5 years post-diagnosis. The fibrosis seen in

[1] Prof., Department of Integrative Medicine, Huashan Hospital, Fudan University, Shanghai-China.
[2] Prof., Institutes of Integrative Medicine, Fudan University, Shanghai-China
[3] Prof., Medical school of HexiCollege, Zhangye, Gansu-China.
E-mail: weiying_acup@126.com
DOI No:10.5505/anadolutd.2023.85057
Geliş Tarihi/Received:01/09/2023 Kabul Tarihi/Accepted: 30/09/2023

IPF generally follows a progressive course, proving unresponsive to current pharmaceutical interventions, and inevitably culminates in respiratory failure due to the obliteration of functional alveolar units. This condition becomes a pressing unmet medical necessity, necessitating urgently needed innovative and comprehensive therapeutic strategies.

Currently, glucocorticoids and immunosuppressants constitute the primary pharmacological agents employed in the clinical management of PF; however, their effectiveness is restricted and they carry the risk of significant side effects. Traditional Chinese medicines hold considerable research significance and offer potential for clinical use in combating PF. In recent times, an increasing number of scientific investigations have focused on harnessing traditional Chinese medicine to ameliorate or mitigate PF, yielding notable advancements in this realm.

Therefore, a bibliometric analysis of Chinese medicine in the context of PF becomes imperative to gain insights into key areas of focus, the evolution of the field's paradigm, forthcoming research trends, the application of Chinese medicine, and a more precise comprehension of treatable mechanisms involving PF and specific Chinese medicine components. Utilizing this bibliometric review, we aim to summarize the progress within this domain, shifts in the prevailing paradigm, prominent subjects across different timeframes, and the anticipated trajectory of Chinese medicine in addressing PF.

Between 2005 and 2023, a total of 395 records are indexed in the Web of Science through a targeted search employing terms such as "Chinese medicine" and "pulmonary fibrosis" within titles, abstracts, or index terms. Scientometrics, as a facet of informatics, enables the examination of patterns within scientific literature to enhance comprehension of emerging trends and the knowledge framework of a given research realm. Tools for scientific mapping utilize scientific literature publications as input, generating interactive visual representations that facilitate exploratory analysis of complex structures and statistical trends. Most such tools are widely accessible (3). Notably, science mapping tools like Ingenuity Pathway Analysis and Cytoscape exhibit parallels to their counterparts in biomedicine research (4, 5). The concept of co-citation analysis fosters the development of diverse science mapping techniques. Representing the intellectual knowledge structure via networks of co-cited references, these techniques are processed by science mapping tools like VOSviewer, DIVA, HistCite, LoetLeydesdorff's software, Network WorkBench, and CiteSpace (6-14). In this review, we employ CiteSpace to delineate the structure and progression of Chinese medicine's application in PF. CiteSpace is purposefully designed to identify sudden shifts and emergent patterns in scientific literature, thus providing an effective and dynamic means to discern various primary domains within the developmental process and explore multiple potential research directions for Chinese medicine in addressing PF.

2. MATERIALS AND METHODS

2.1 CiteSpace and VOS viewer

CiteSpace is utilized to create and assess networks composed of co-cited references, utilizing bibliographic records procured from the Web of Science. The functionality of the VOS viewer proves particularly advantageous in constructing visual representations of authors or journals based on co-citation data, as well as forming maps of keywords through the analysis of co-occurrence data (6). An initial search centered around the topics of "Chinese medicine" and "pulmonary fibrosis" yielded a total of 395 publications published between 2005 and 2023. Following the removal of duplicated entries and less representative types of records, including corrections, editorial materials, letters, meeting abstracts, news pieces, notes, and proceeding papers, the dataset was streamlined to encompass 389 original research articles and review papers. It's important to note that the compilation of 389 records excludes relevant publications in cases where the term "Chinese medicine" or "pulmonary fibrosis" does not explicitly appear within the titles, abstracts, or item descriptions.

2.2 Data acquisition and processing

All publications were sourced from the Web of Science core collection. The search strategy employed was as follows: (ALL=("pulmonary fibrosis")) AND ALL=("Chinese medicine"); the search encompassed indexes from the Web of Science core collection, including Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), Arts and Humanities Citation Index (A&HCI), Proceedings Citation Index Science (CPCI-S), Book Citation Index– Science (BKCI-S), Emerging Sources Citation Index (ESCI), Conference Proceedings Citation Index Social Science & Humanities (CPCI-SSHI), and Book Citation Index– Social Sciences & Humanities (BKCI-SSH). The timeframe considered was 2005–2023, with a slice length of 1 year. The correlation strength was assessed using cosine, and a threshold was applied to each time slice, selecting the Top N = 25. Both CiteSpace and VOS viewer were employed to analyze the comprehensive network structure, the clusters within the network, interconnections between these clusters, pivotal nodes, and pathways. Each node on the map represented a specific type of study under analysis, while links between nodes illustrated associations, collaborations, co-occurrences, or co-citations. Furthermore, several indicators were calculated to gauge the impact and significance of

publications or key terms, including betweenness centrality (a concept identifying highly important nodes, where values exceeding 0.1 designate key nodes) and sigma values computed from centrality and emergence burst measurements, indicating significance in structural alterations and citations. In CiteSpace, nodes represented different time periods using varying colors in modes resembling tree ring history, spanning 2005–2023. In the label view of VOS viewer or the cluster view of CiteSpace, colors indicated the assigned cluster derived from the clustering technique applied. Additionally, in the density view of VOS viewer, the color of a point on the map denoted the quantity of items in its vicinity and the significance of neighboring items.

3. RESULTS

3.1 Annual growth trend

A total of 389 publications were identified through a search conducted in the Web of Science Core Collection. The annual publication and citation figures are depicted in Figure 2. The overall pattern of both metrics reflects steady growth. Notably, during the years spanning 2007 to 2015, the yearly count of publications pertaining to Chinese medicine for PF exhibited fluctuations while largely remaining consistent. In the late 2000s and early 2010s, the count of English-language research articles and citations concerning Chinese medicine for PF remained consistently low. The most significant surge in publications occurred in 2022 (n=108), and likewise, the peak in citations was also recorded in 2022 (n=1141). This suggests an escalating interest in Chinese medicine for PF. The most remarkable shifts in citations were observed between 2020 and 2022, and in publications between 2019 and 2020, as well as between 2021 and 2022. Each of these ascending trends may signify a paradigm shift in recognizing the application of acupuncture therapy for asthma or the exploration of underlying mechanisms. The subsequent section will delve into a detailed analysis of each trend.

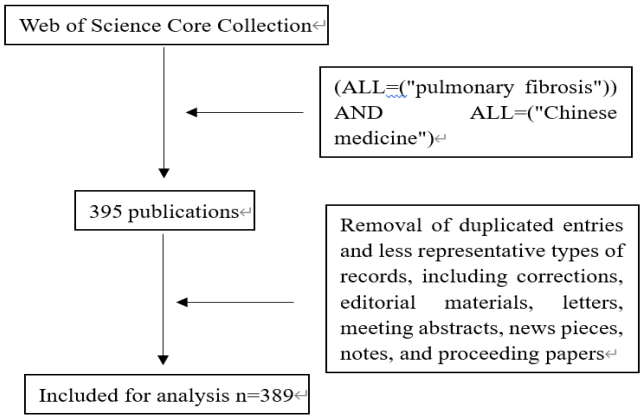

Figure 1: Flow chart of data acquisition and progressing

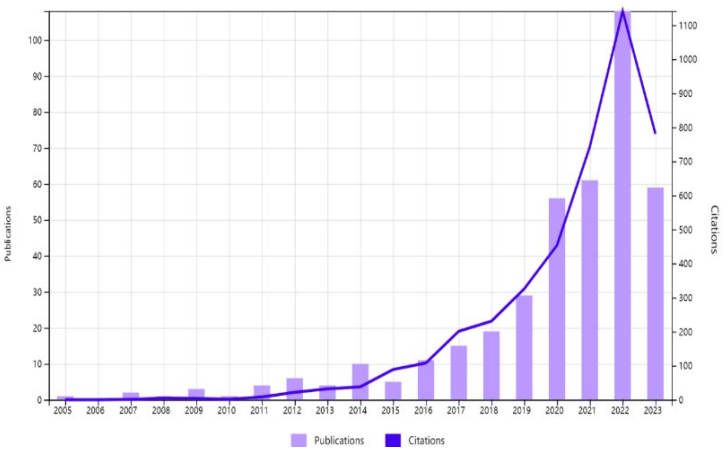

Figure 2: The trend of publications and citations about Chinese medicine for pulmonary fibrosis (PF)

3.2 Distribution of countries/regions and organizations

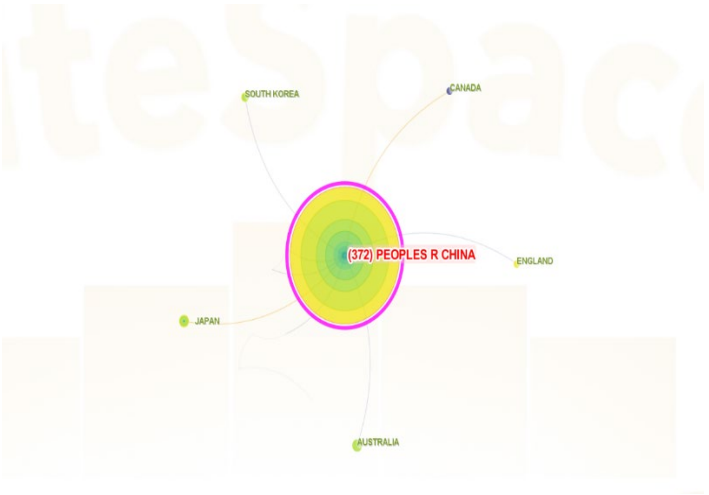

Figure 3: Map of countries researching Chinese medicine for PF

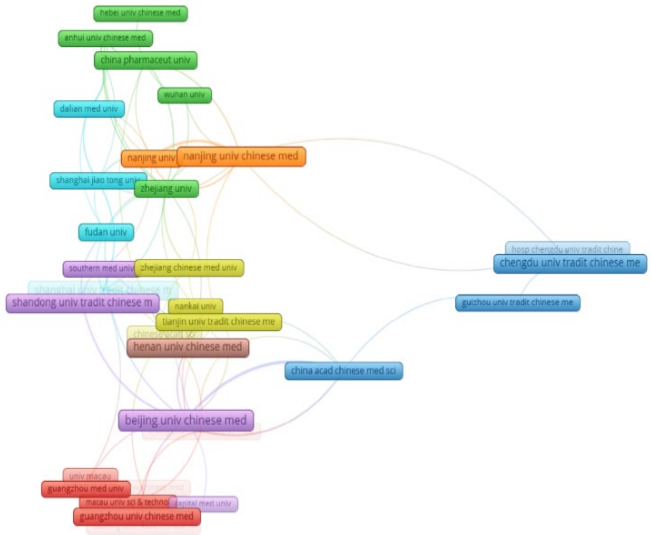

Figure 4: Map of organizations researching Chinese medicine for PF

Table 1: The top five countries with the highest centrality

	country/region	count	centrality
1	PEOPLES R CHINA	372	0.91
2	GERMANY	3	0.46
3	ITALY	2	0.34
4	TAIWAN	8	0.19
5	USA	13	0

Table 2: The top 8 organizations with the highest centrality

	count	centrality	organization
1	22	0.28	Shanghai University of Traditional Chinese Medicine
2	12	0.27	Chinese Academy of Sciences
3	45	0.24	Beijing University of Chinese Medicine
4	14	0.15	Fudan University
5	33	0.11	Nanjing University of Chinese Medicine
6	20	0.11	Shandong University of Traditional Chinese Medicine
7	18	0.11	China Academy of Chinese Medical Sciences
8	14	0.11	Zhejiang University

A collective total of 389 articles originated from 16 distinct countries/regions and 395 organizations. As illustrated in Figure 3 using CiteSpace, China emerged as the foremost contributor with the highest number of articles (n=372), trailed by the United States (n=13) and Taiwan China (n=8). However, the centrality score for the United States was 0, which is lower than that of China (centrality=0.91), Germany (centrality=0.46), Italy (centrality=0.34), and Taiwan China (centrality=0.19). These four pivotal nodes play a bridging role in the realm of studies on Chinese medicine for pulmonary fibrosis. Articles originating from these countries may potentially usher in new paradigms for recognizing the application of Chinese medicine in addressing pulmonary fibrosis, illuminating novel pathogenic mechanisms, targets, and regulatory networks associated with the condition through the lens of Chinese medicine research, or revealing specific implementations of Chinese medicine to benefit pulmonary fibrosis patients. In Figure 4, displayed by VOS viewer, label sizes are determined by item weight, representing links between different institutions. A larger label and circle indicate a higher weight for an item. The color assigned to an item corresponds to its cluster membership. Lines connecting items signify links, with up to 1000 of the strongest links displayed by default. The spatial separation between two organizations in the visualization provides an approximation of their interconnectedness in terms of co-authorship links. Generally, closer placement indicates stronger relatedness. While Beijing University of Chinese Medicine emerged as the most prolific institution (n=45), its centrality remained relatively moderate (centrality=0.24). In contrast, Shanghai University of Traditional Chinese Medicine (n=22, centrality=0.28) and Chinese Academy of Sciences (n=12, centrality=0.27) boasted higher centrality scores.

3.3 Authors and co-cited authors

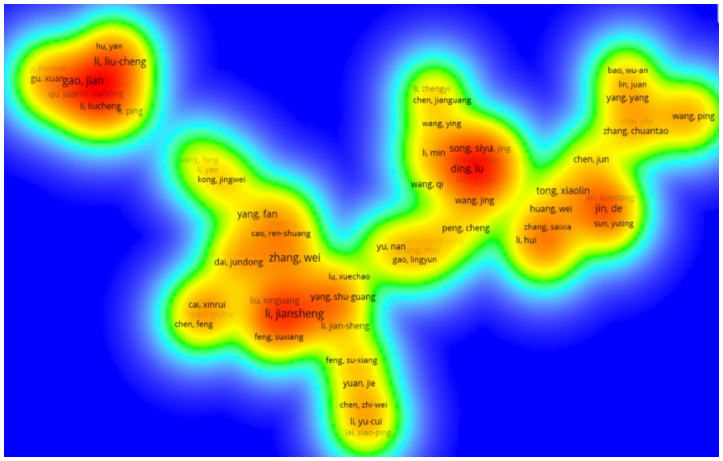

Figure 5: The authorship of authors

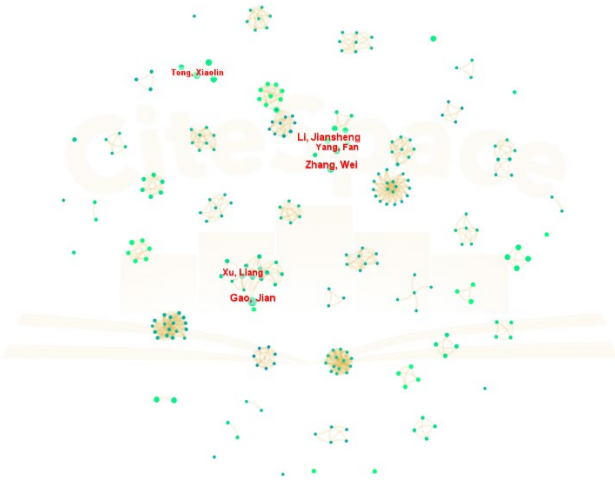

Figure 6: The co-citation analysis of authors

Table 3: The top 5 authors with the most citations

Rank	Author	Citations	Documents	total link strength
1	Jian, Gao	522	11	63
2	Liucheng, Li	435	8	21
3	Liang, Xu	295	7	47
4	Wei Zhang	162	10	12
5	Xiaolin, Tong	87	6	33

As depicted in Figure 5 through the utilization of VOS viewer, a comprehensive count of 2334 authors were actively engaged in research concerning acupuncture therapy for asthma. Within this cohort, 377 authors contributed to the field by publishing at least two articles. Notably, Jian Gao emerged as the leading contributor in terms of articles related to Chinese medicine for pulmonary fibrosis (n=11), closely followed by Jiansheng Li and Wei Zhang (n=10) (Figure 5). Jian Gao, with a notable publication count of 63, showcased the strongest link strength, maintaining a consistent and close association across their research endeavors. A similar consistent link was observed in a series of research endeavors involving Jiansheng Li (n=10) and Lu Ding (n=5) (Figure 5; Table 2).

Co-citation analysis spotlighted the most frequently cited references, with authorship attributed to Jian Gao (n=522) taking the lead, followed by Liucheng Li (n=435) and Liang Xu (n=296) (Figure 6; Table 2). The co-citation analysis of authors depicted in Figure 6 was conducted utilizing CiteSpace.

3.4 Journals and co-cited journals

Between 2005 and 2023, a total of 389 scholarly journals disseminated articles pertaining to Chinese medicine's application in addressing pulmonary fibrosis. In the visualization, citing journals are positioned on the left, while cited journals appear on the right, visually connected by colored pathways representing citation relationships. The circular shapes denote specialized research fields characterized by a substantial number of articles and authors. The dimensions of these circles convey the author-article ratios, where the ratio between width and height offers insight. Emphasis is placed on lines denoting connections of greater significance in comparison to others.

For instance, a closer co-citation relationship is observed between publications in journals encompassing themes of "molecular biology, immunology" and those focused on "health, nursing, medicine," or "molecular biology, genetics." The top 5 journals, noted for both citation count and centrality, are presented in Table 4 (Table 4).

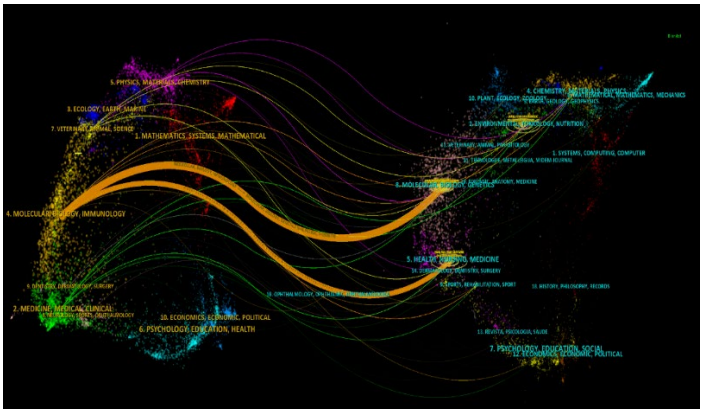

Figure 7: The dual map overlay of journals related to Chinese medicine for PF

Table 4: The collection table formed by the top 5 journals with the most citation count and centrality

citation counts	journal	centrality	journal
201	AM J RESP CRIT CARE	0.89	AM J RESP CELL MOL
173	J ETHNOPHARMACOL	0.34	ACTA VIROL
171	PLOS ONE	0.19	AM J RESP CRIT CARE
149	SCI REP-UK	0.19	AM J PHYSIOL-LUNG C
137	LANCET	0.15	AM REV RESPIR DIS

3.5 Co-citied references analysis

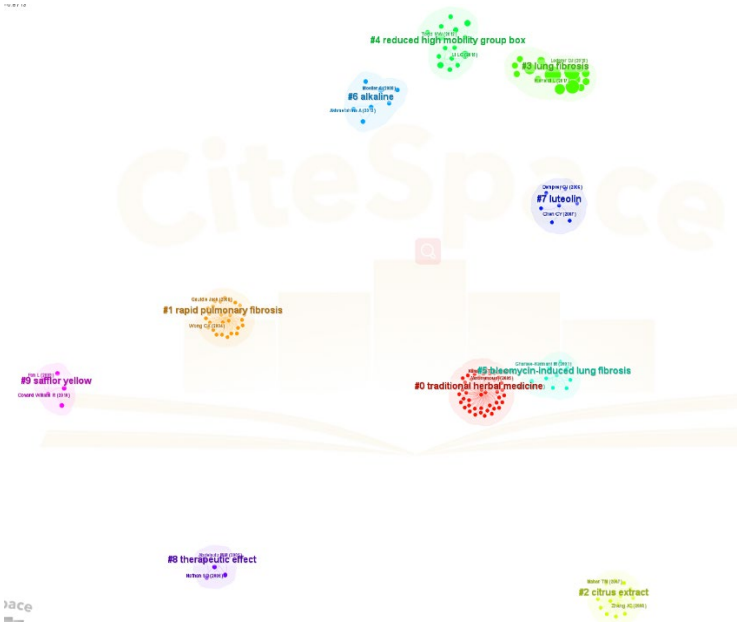

Figure 8: The cluster of co-cited references associated with Chinese medicine for PF

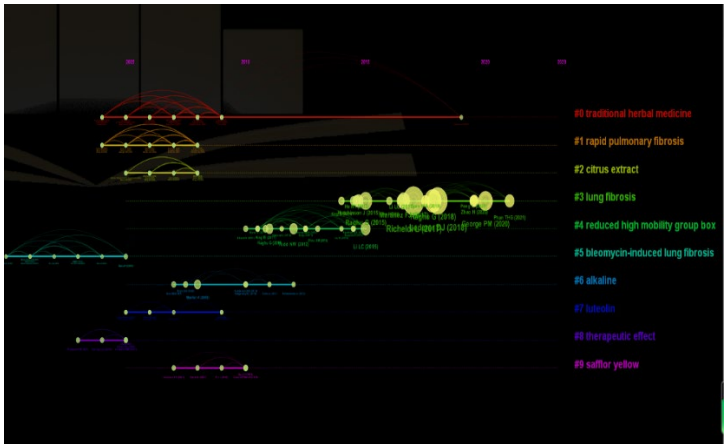

Figure 9: Timeline view of co-cited references associated with Chinese medicine for

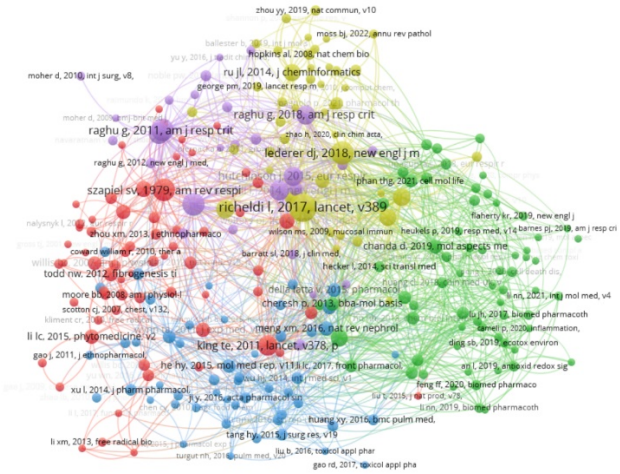

Figure 10: Co-cited references analyzed by VOS viewer

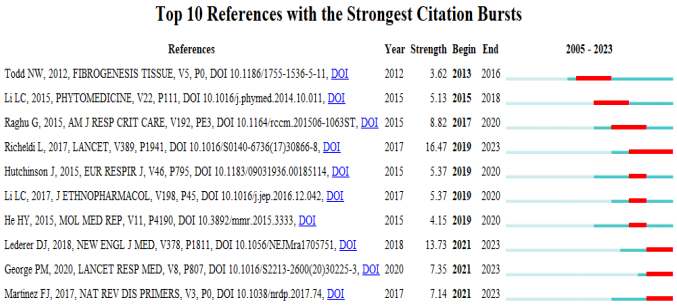

Figure 11: The top 10 references with the strongest citation bursts

Table 5: The collection of the top 10 cited references with the most count and centrality

	count	reference	centrality	reference
1	42	Richeldi L, 2017, LANCET, V389, P1941, DOI 10.1016/S0140-6736(17)30866-8	0.07	Brinker AM, 2007, PHYTOCHEMISTRY, V68, P732, DOI 10.1016/j.phytochem.2006.11.029
2	37	Lederer DJ, 2018, NEW ENGL J MED, V378, P1811, DOI 10.1056/NEJMra1705751	0.07	Ask K, 2008, J TRANSL MED, V6, P0, DOI 10.1186/1479-5876-6-16
3	25	Raghu G, 2018, AM J RESP CRIT CARE, V198, PE44, DOI 10.1164/rccm.201807-1255ST	0.07	CHEN JL, 2009, CLIN EXP ME IN PRESS, V0, P0
4	21	George PM, 2020, LANCET RESP MED, V8, P807, DOI 10.1016/S2213-2600(20)30225-3	0.06	Li LC, 2015, PHYTOMEDICINE, V22, P111, DOI 10.1016/j.phymed.2014.10.011
5	16	Raghu G, 2015, AM J RESP CRIT CARE, V192, PE3, DOI 10.1164/rccm.201506-1063ST	0.06	Xiao JH, 2005, PLANTA MED, V71, P225, DOI 10.1055/s-2005-837821
6	15	Martinez FJ, 2017, NAT REV DIS PRIMERS, V3, P0, DOI 10.1038/nrdp.2017.74	0.05	Raghu G, 2015, AM J RESP CRIT CARE, V192, PE3, DOI 10.1164/rccm.201506-1063ST
7	9	Li LC, 2015, PHYTOMEDICINE, V22, P111, DOI 10.1016/j.phymed.2014.10.011	0.04	Richeldi L, 2017, LANCET, V389, P1941, DOI 10.1016/S0140-6736(17)30866-8
8	9	Li LC, 2017, J ETHNOPHARMACOL, V198, P45, DOI 10.1016/j.jep.2ccc016.12.042	0.03	King TE, 2011, LANCET, V378, P1949, DOI 10.1016/S0140-6736(11)60052-4
9	9	Hutchinson J, 2015, EUR RESPIR J, V46, P795, DOI 10.1183/09031936.00185114	0.03	Moore BB, 2008, AM J PHYSIOL-LUNG C, V294, PL152, DOI 10.1152/ajplung.00313.2007
10	8	Phan THG, 2021, CELL MOL LIFE SCI, V78, P2031, DOI 10.1007/s00018-020-03693-7	0.01	Lederer DJ, 2018, NEW ENGL J MED, V378, P1811, DOI 10.1056/NEJMra1705751

Out of the 12,757 cited references, 258 garnered citations of at least 5 instances. These 258 publications, entailing 9,978 connections, were segregated into five clusters, as portrayed in Figure 10. The aggregate link strength amounted to 13,733. As evidenced in Figure 9, clusters 5 (pertaining to bleomycin-induced lung fibrosis) and 8 (focusing on therapeutic effects) emerged earlier in the timeline. In contrast, cluster 4 (centered on lung fibrosis) is an ongoing development that could potentially evolve into a future hotspot (Figure 8).

The top 10 references characterized by the most robust citation bursts are itemized in Figure 11. The most potent burst (strength=16.47) emanated from a paper titled "Idiopathic pulmonary fibrosis," published in Lancet by Richeldi L et al. in 2017, with its burst spanning from 2019 to 2023. This article provided an all-encompassing overview of the presentation, pathophysiology, diagnosis, and available treatment alternatives for individuals grappling with idiopathic pulmonary fibrosis (1). The revelations regarding the comprehension of underlying mechanisms responsible for lung fibrosis through this work bear the potential to revolutionize the management of patients afflicted by various progressive fibrotic lung disorders.

Table 5 furnishes the top 10 cited references, considering both count and centrality metrics. Notably, the article with the most robust burst also ranks as the most co-cited reference. Among these, the reference boasting the highest centrality was published in Phytochemistry by Brinker AM et al. in 2007, entitled "Medicinal chemistry and pharmacology of genus Tripterygium." This publication provides an in-depth exploration of the biochemical constitution, along with the biological and pharmacological functions, of Tripterygium extracts, focusing on their principal bioactive components (15).

3.6 Keyword analysis of trending research topic

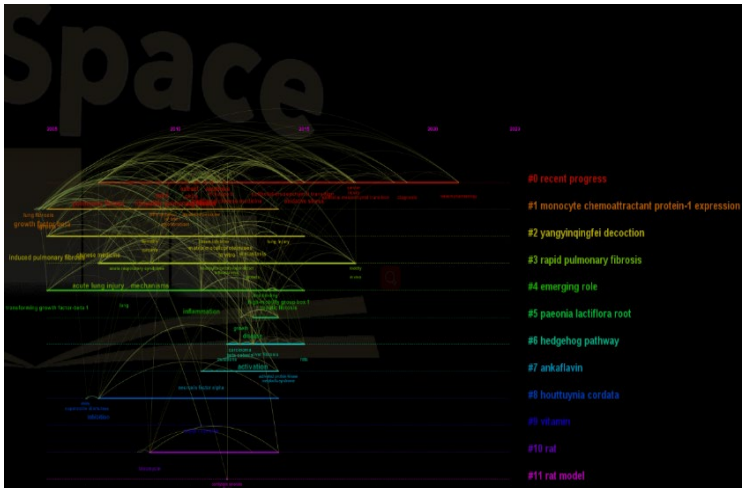

Figure 12: The timeline view of keywords associated with Chinese medicine for PF

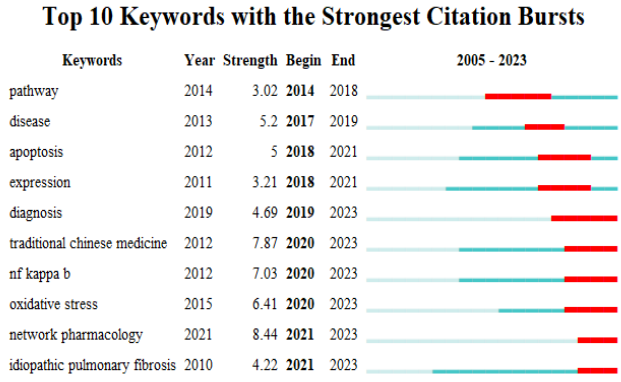

Figure 13: The top 8 keywords with the strongest citation bursts

Table 6: Summary of the largest 12 clusters of keywords analysis

ClusterID	Size	Silhouette	Label (LSI)	Label (LLR)	Label (MI)	Average Year
0	46	0.654	idiopathic pulmonary fibrosis	recent progress (55.04, 1.0E-4)	ankaflavin (7.41)	2013
1	34	0.889	transforming growth	monocyte chemoattractant protein-1 expression (40.91, 1.0E-4)	idiopathic pulmonary fibrosis (0.04)	2009
2	30	0.88	promising natural agent	yangyinqingfei decoction (37.1, 1.0E-4)	gut microbe bacteroide (0.03)	2011
3	24	0.882	bleomycin-induced pulmonary fibrosis	rapid pulmonary fibrosis (55.73, 1.0E-4)	akt signaling pathway (0.09)	2011
4	18	0.91	bleomycin-induced pulmonary fibrosis	emerging role (49.94, 1.0E-4)	ankaflavin (0.09)	2013
5	17	0.928	fibrotic diseases	paeonialactiflora root (31.66, 1.0E-4)	bleomycin-induced pulmonary fibrosis (0.05)	2013
6	16	0.89	protective effect	recent progress (63.39, 1.0E-4)	ankaflavin (0.28)	2013
7	15	0.953	treatment of metabolic syndrome with ankaflavin, a secondary metabolite isolated from the edible fungus monascus spp.	ankaflavin (14.88, 0.001)	bleomycin-induced pulmonary fibrosis (0.06)	2013
8	13	0.956	protective effect	houttuynia cordata (25.27,	bleomycin-induced pulmonary	2009

Table 7: The collection table formed by the top 10 keywords with the most count and the highest centrality

	keyword	count	keyword	centrality
1	pulmonary fibrosis	153	induced pulmonary fibrosis	0.29
2	idiopathic pulmonary fibrosis	86	growth factor beta	0.28
3	expression	62	gene expression	0.21
4	traditional chinese medicine	52	activation	0.21
5	oxidative stress	49	pulmonary fibrosis	0.18
6	activation	48	cells	0.17
7	inflammation	35	acute lung injury	0.16
8	induced pulmonary fibrosis	35	inflammation	0.16
9	mechanisms	30	inhibition	0.15
10	nf kappa b	27	chinese medicine	0.15

In total, 1924 keywords were extracted. As depicted in Table 7, "pulmonary fibrosis" emerged as the most commonly occurring keyword (n=153), closely followed by "idiopathic pulmonary fibrosis" (n=86) and "expression" (n=62). The top 10 keywords with the highest betweenness centrality values all exceeded 0.1, as highlighted in Table 7.

The most substantial cluster, designated as Cluster #0, comprises 46 members and boasts a silhouette value of 0.654. It is identified as encompassing recent advancements by LLR, idiopathic pulmonary fibrosis according to LSI, and ankaflavin (7.41) based on MI. Notably, the key referencing article within this cluster is authored by Cui, W (2015.0), titled "Total glycosides of yupingfeng protects against bleomycin-induced pulmonary fibrosis in rats associated with reduced high mobility group box 1 activation and epithelial-mesenchymal transition"(16). Among the highly cited members within this cluster are topics such as pulmonary fibrosis, idiopathic pulmonary fibrosis, and expression.The second most substantial cluster, referred to as Cluster #1, comprises 34 members and possesses a silhouette value of 0.889. It is characterized by LLR as monocyte chemoattractant protein-1 expression, labeled as transforming growth by LSI, and identified as idiopathic pulmonary fibrosis (0.04) via MI. A pivotal citing article within this cluster is attributed to Shen, Y (2005.0), titled "Feitai, a Chinese herbal medicine,

reduces transforming growth factor-beta 1 and monocyte chemoattractant protein-1 expression in bleomycin-induced lung fibrosis in mice"(17). Prominent members encompass transforming growth factor beta (tgf beta), growth factor beta, and myofibroblast.The third prominent cluster, recognized as Cluster #2, encompasses 30 members and possesses a silhouette value of 0.88. LLR labels it as yangyinqingfei decoction, LSI designates it as a promising natural agent, and MI identifies it with gut microbe Bacteroides (0.03). The principal citing article within this cluster is credited to An, SM (2013.0), titled "Stem cell signaling as a target for novel drug discovery: recent progress in the Wnt and Hedgehog pathways"(18). Notable members within this cluster involve induced pulmonary fibrosis, Chinese medicine, and in vitro approaches (Table 6).

The most robustly bursted keywords, totaling eight, are illustrated in Figure 12. "Network pharmacology" emerged as the keyword with the most potent citation burst (strength=8.44). Observing Figure 11, it becomes evident that the subject of "recent progress" within Cluster 0 remains an active and ongoing area of research (Figure 11).

4. DISCUSSION

Utilizing data sourced from the Web of Science Core Collection spanning 2005 to 2023, a comprehensive compilation of 389 articles concerning Chinese medicine for PF found publication across 389 scholarly journals. These contributions were authored by 2334 individuals affiliated with 395 organizations hailing from 16 different countries or regions. The evident rise in publication volumes signifies an escalating focus on this subject, indicating a growing surge of interest in the field.

With an extensive history spanning over 5000 years, herbal medicine has held a central and pivotal role in medical practices across diverse regions of Asia. Hence, the extensive application of traditional and herbal medicine in addressing PF is entirely expected. The impact of Traditional Chinese Medicine (TCM) on PF therapy remains of paramount importance as it embodies the essence and significance for subsequent research endeavors. This pivotal role aligns seamlessly with the insights derived from the bibliometric analysis of co-cited references. The most extensive cluster, Cluster #0, comprises 47 members and boasts a silhouette value of 1. It is labeled as "traditional herbal medicine" by LLR, "how useful is traditional herbal medicine for pulmonary fibrosis?" according to LSI, and "pulmonary fibrosis" based on MI. A key referencing article within this cluster is authored by Yang, J (2009.0), titled "How useful is traditional herbal medicine for pulmonary fibrosis?"(19).

Numerous clinical studies involving traditional remedies have been conducted to explore the impact of TCM onPF. For instance, one study investigating the effects of Qi-hong decoction enrolled 60 patients diagnosed with true IPF from two medical centers in Beijing, China (20). Patient recruitment adhered to diagnostic criteria established by the Chinese Society of Respiratory Diseases in a document dated 2002, which was aligned with ATS/ERS guidelines. Patients were randomly divided in a 1:1 ratio to receive either Qi-hong decoction or prednisone for a 3-month duration, following a prospective but not double-blind approach. Notably, patients receiving Qi-hong decoction exhibited a statistically significant improvement in predicted DLco (diffusing capacity of the lungs for carbon monoxide) compared to the prednisone group (mean change from baseline +7.02% vs +3.15%). At the conclusion of the study, both groups reported two patient deaths each, while the Qi-hong decoction group displayed a lower frequency of pulmonary infections.

Another prospective trial enrolled 100 IPF patients to evaluate the effectiveness of Tao-er-dan decoction (21). IPF diagnoses were confirmed according to an earlier version of the diagnostic criteria outlined by the Chinese Society of Respiratory Disease (from 1994). The patients were randomly assigned to receive either Tao-er-dan decoction in addition to standard therapy with prednisone/cyclophosphamide (n=68) or solely prednisone/cyclophosphamide (n=32) for a span of 6 months. The primary endpoint was the survival rate one year post-randomization, which exhibited no significant divergence between the two groups (1-year survival in Tao-er-dan decoction: 88% vs control: 78%). Nonetheless, statistically significant differences emerged between the groups in terms of 3-year (59% vs 37%) and 5-year (37% vs 12%) survival rates, even though the patient numbers at these time points were relatively limited and the clinical significance of these findings remains uncertain. Nonetheless, the treatment's influence on survival appears to be noteworthy.

The effectiveness of Bu-Shen-Yi-Fei-Decoction was assessed in patients afflicted with PF secondary to rheumatoid arthritis (22). In this study, a total of 38 patients were randomly allocated to either receive Bu-Shen-Yi-Fei-Decoction in combination with prednisone or prednisone alone [22]. The findings revealed that the combination of Bu-Shen-Yi-Fei-Decoction and prednisone led to a significant improvement in the mean change from baseline of the predicted values of TLC (+8.65% for Bu-Shen-Yi-Fei-Decoction vs +2.90% for prednisone), VC (vital capacity, +7.07% for Bu-Shen-Yi-Fei-Decoction vs +3.06% for prednisone), and DLco (+8.33% for Bu-Shen-Yi-Fei-Decoction vs +4.55% for prednisone) after a 6-month treatment period.

To delve deeper into the therapeutic mechanisms of Chinese medicine for PF, it was imperative to conduct animal experiments employing a robust PF animal

model. This approach was validated by the bibliometric analysis of co-cited references, affirming the logical progression of this research avenue. The second most prominent cluster, labeled as Cluster #1, encompasses 28 members and demonstrates a silhouette value of 1. LLR identifies it as "rapid pulmonary fibrosis," LSI designates it as "rapid pulmonary fibrosis induced by acute lung injury via a lipopolysaccharide three-hit regimen," and MI associates it with "pulmonary fibrosis." A pivotal referencing article within this cluster is attributed to Li, H in 2009(23). Remarkably cited members within this cluster include contributions by Gauldie Jack, Wong CK, and Glass WG (24-26).

The references cited within both this cluster and cluster 5 (bleomycin-induced lung fibrosis) afforded us a perspective and framework through which to grasp the innovative approaches to animal modeling. Notably, the most significantly cited work within this context was authored by Glass WG and titled "Mechanisms of Host Defense following Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) Pulmonary Infection of Mice." This reference precisely detailed the replication of the pulmonary fibrosis model induced by SARS-CoV, thus contributing to our understanding of the process of the alteration of PF animal model. The work authored by Gauldie Jack elucidated the sequential changes in both TGF-β and the Smad signaling pathway within experimental models. This article established a widely accepted and prevalent paradigm for validating the pathway within experimental models.

Cluster 5 articles presented a conventional framework for investigating the impact of Chinese medicine on PF using animal models. The predominant reference cited within this cluster was authored by Yun Shen, titled "Feitai, a Chinese herbal medicine, reduces transforming growth factor-beta 1 (TGF-β1) and monocyte chemoattractant protein-1(MCP-1) expression in bleomycin (BLM)-induced lung fibrosis in mice." This article delineated how Feitai treatment contributes to the mitigation of lung fibrosis induced by BLM, partly through the suppression of MCP-1 and TGF-β1 expression(17).

Within the third most substantial cluster, the pertinent references commence delving into the efficacy of herbal medications. This segment holds pivotal significance within our review pertaining to Chinese medicine for PF. Notably, the article that garners the most citations within this cluster is authored by Zhou XM and bears the title "Inhibitory effects of citrus extracts on the experimental pulmonary fibrosis" (27). This article aims to unveil the anti-pulmonary fibrosis impact of the ethanol extract derived from Citrus reticulata.

Furthermore, once the PF animal model has reached a mature stage of development, an array of animal experiments is conducted to substantiate the therapeutic efficacy of various monomers sourced from Chinese herbal medicine or traditional Chinese formulas, as demonstrated in cluster 8. A prominent citing article within this context is authored by Hongqi Zhang, titled "Therapeutic effect of Chinese medicine formula DSQRL on experimental pulmonary fibrosis." The outcomes of this study revealed a substantial positive therapeutic outcome for experimental PF through treatment with the Chinese medicine DSQRL. Moreover, the article reported minimal side effects attributed to DSQRL administration. The rats treated with DSQRL exhibited superior growth rates and overall conditions compared to the prednisone group. When analyzing the group subjected to combined prednisone and DSQRL treatment, akin therapeutic benefits were observed as with DSQRL monotherapy. This manifested in noteworthy improvements in both BAL analysis and hydroxyproline assays. However, the body weight of rats within the combined treatment group was comparable to that of the prednisone group, but significantly lower than that of the control and DSQRL groups. These findings suggest that the adverse general conditions observed in treatment were likely linked to prednisone, while DSQRL potentially counteracted the detrimental impact of CCl_4 toxicity and adverse effects associated with prednisone treatment. This underscores the holistic approach of TCM in treating patients rather than solely addressing the disease(28).

Based on the analysis of keywords and co-cited references, we have compiled a summary of the prominent individual components or formulas from TCM that have been substantiated for their therapeutic efficacy in addressing PF. As an illustration, the administration of glycoside of Yupingfeng (YPF-G) at various dosages demonstrated a substantial reduction in both BLM-induced alveolitis and PF in rat models. Furthermore, there was a notable decrease in the levels of high mobility group protein 1(HMGB1), laminin, hyaluronic acid, and hydroxyproline. In parallel, the heightened protein expression of HMGB1, along with the mesenchymal markers vimentin and alpha-smooth muscle actin, as well as the diminished protein expression of the epithelial marker E-cadherin, exhibited significant inhibition following treatment with YPF-G(16). In addition, HMGB1 has the capacity to induce autophagy through the release of the pivotal autophagic gene Beclin 1 from its BCL-2 complex (29). Therefore, it is imperative to delve deeper into the potential role of autophagy in the context of pulmonary fibrosis, warranting further investigation.

Feitai was proven to suppress TGF-β1 and MCP-1 expression in BLM-induced lung fibrosis. The TGF-β1 signaling pathway assumes a critical role in instigating and driving the pathogenesis of PF. This signaling mechanism not only down-regulates peroxisome biogenesis but also curtails the metabolic activity of

these organelles in PF-associated fibroblasts. In vitro observations conducted through cell culture experiments involving human fibroblasts and lung tissue corroborated these findings, revealing a significant reduction in peroxisomal biogenesis and metabolic protein levels within the lungs of transgenic mice expressing a constitutively active TGF-β type I receptor kinase (ALK5) at one month of age. Conversely, peroxisome biogenesis protein, exemplified by peroxisomal membrane protein Pex13p (PEX13p), as well as peroxisomal lipid metabolic enzyme peroxisomal acyl-coenzyme A oxidase 1 (ACOX1), and the antioxidative enzyme catalase, exhibited substantial up-regulation in TGF-β type II receptor and Smad3 knockout mice. A novel mechanism involving the interaction of the Smad3 transcription factor with the PEX13 gene was unveiled via chromatin immunoprecipitation–on–chip assays. This mechanism was also corroborated within a BLM-induced PF model applied to TGF-β type II receptor knockout mice. Through Smad-dependent signaling, TGF-β1 actively participates in the regulation of peroxisomal biogenesis and metabolism. These findings introduce fresh avenues for the development of therapeutic strategies aimed at inhibiting the progression of PF among affected patients (30).

The pursuit of novel drug discovery targets for PF therapy has underscored the potential involvement of stem cell signaling pathways, which appear to exhibit responsiveness to traditional Chinese medicines. Compounds derived from herbal sources might interact selectively with components of stem cell signaling pathways, displaying notable affinities. Given that numerous of these phenomena can be elucidated through molecular interactions, these observations hint at the promising prospect of deriving stem cell-targeting drugs from natural products with remarkable success. Within the realm of stem cell signaling pathways, several drug targets have been pinpointed, with WNT and Hedgehog emerging as the two most pivotal signaling pathways(18).

Numerous investigations have been dedicated to exploring the antioxidative properties of Houttuynia cordata (HC) and its potential safeguarding impact against BLM-induced PF in rat models. The findings revealed a varied extent of antioxidant activities exhibited by the aqueous extract of HC across all assessed model systems. While HC demonstrated comparatively milder capabilities in scavenging free radicals and inhibiting xanthine oxidase in comparison to vitamin E, its effectiveness in mitigating lipid peroxidation in rat liver homogenate closely approached that of vitamin E. In the context of animal studies, HC exhibited a significant reduction in levels of superoxide dismutase, malondialdehyde, hydroxyproline, interferon-γ, and tumor necrosis factor-α. Notably, an elevation in catalase concentration was observed in bronchoalveolar lavage fluid. Moreover, HC visibly ameliorated the morphological appearance of lungs in BLM-treated rats. These outcomes collectively indicate that HC holds a protective capacity against BLM-induced PF, with this safeguarding effect being notably more pronounced than that attributed to vitamin E. In conclusion, the shielding influence of HC on PF may stem, at least in part, from its ability to curtail oxidative damage incurred by BLM (31). HC was also proven to up-regulate IFN-γ and inhibit the TGF-β1/Smad pathway(32).

A comparative investigation was undertaken to assess the distinct impacts of various Chinese herbal components on PF therapy. As an example, a particular study aimed to scrutinize the disparities in the effects of Ephedra sinica Stapf and Fructus Schisandrae Chinensis in relation to angiogenesis for the treatment of rat IPF induced by BLM (33).

Within a fibrotic cell model prompted by the induction of TGF- β 1, the human lung epithelial A549 cells underwent a transition toward a mesenchymal phenotype, resulting in an upsurge of vimentin expression and a corresponding reduction in E-cadherin levels. Notably, this epithelial-mesenchymal transition displayed partial reversibility upon exposure to cordycepin, a principal constituent of Cordyceps(34).

The effects of DangguiBuxue Tang (DBT) were observed in mitigating BLM-induced PF in rats. The current investigation affirms that DBT, specifically the modified form DBTG, counteracts BLM-induced PF by regulating oxidative stress levels through the suppression of NOX4(35).

It has been demonstrated that Angelica sinensis has the capacity to modulate matrix metalloproteinases/tissue inhibitors of MMPs (MMPs/TIMPs) and TGF-β1(36). The involvement of MMPs and their counterparts TIMPs, in the progression of PF has been recognized for many years(37). Furthermore, as previously mentioned, the role of TGF-β1 also holds significant importance in the context of PF.

5. CONCLUSION

In summary, this study offers valuable insights into potential collaborations among researchers, institutions, and different regions or countries. It also highlights the interrelationships among specific journals, documents the evolutionary progress of Chinese medicine for PF, and outlines current insights into PF mechanisms and therapeutic approaches. Future research endeavors should focus on validating the effectiveness of Chinese medicine for PF through diverse perspectives, identifying novel targets for pharmacological interventions, and integrating precision medicine strategies to effectively address PF pathogenesis.

This study marks the first bibliometric investigation to comprehensively analyze publications pertaining to Chinese medicine for PF. In contrast to conventional reviews, the bibliometric analysis presents an innovative and unbiased perspective on the evolving research priorities and trends. Furthermore, the utilization of multiple bibliometric tools enhances the breadth and depth of the findings. Ultimately, this study raises awareness about the significance of Chinese medicine in PF research and treatment, equips scholars with a holistic view of Chinese medicine's role in PF-related research, and serves as a comprehensive and impartial roadmap for future developments in the field of Chinese medicine for PF.

REFERENCES

1- Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. The Lancet. 2017;389(10082):1941-52.
2- Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. New England Journal of Medicine. 2020;383(10):958-68.
3- Cobo MJ, López-Herrera AG, Herrera-Viedma E, et al. Science mapping software tools: Review, analysis, and cooperative study among tools. Journal of the American Society for information Science and Technology. 2011;62(7):1382-402.
4- Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research. 2003;13(11):2498-504.
5- Jiménez-Marín Á, Collado-Romero M, Ramirez-Boo M, et al., editors. Biological pathway analysis by ArrayUnlock and ingenuity pathway analysis. BMC proceedings; 2009: Springer.
6- Van Eck N, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. scientometrics. 2010;84(2):523-38.
7- Garfield E. Historiographic mapping of knowledge domains literature. Journal of Information Science. 2004;30(2):119-45.
8- Börner K, Huang W, Linnemeier M, et al. Rete-netzwerk-red: analyzing and visualizing scholarly networks using the Network Workbench Tool. Scientometrics. 2010;83(3):863-76.
9- Morris SA, Yen G, Wu Z, et al. Time line visualization of research fronts. Journal of the American society for information science and technology. 2003;54(5):413-22.
10- Leydesdorff L, Schank T. Dynamic animations of journal maps: Indicators of structural changes and interdisciplinary developments. Journal of the American Society for Information Science and Technology. 2008;59(11):1810-8.
11- Chen C, Ibekwe-SanJuan F, Hou J. The structure and dynamics of cocitation clusters: A multiple-perspective cocitation analysis. Journal of the American Society for information Science and Technology. 2010;61(7):1386-409.
12- Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. Journal of the American Society for information Science and Technology. 2006;57(3):359-77.
13- Chen C, Song I-Y, Yuan X, et al. The thematic and citation landscape of data and knowledge engineering (1985–2007). Data & Knowledge Engineering. 2008;67(2):234-59.
14- Chen C. Predictive effects of structural variation on citation counts. Journal of the American Society for Information Science and Technology. 2012;63(3):431-49.
15- Brinker AM, Ma J, Lipsky PE, et al. Medicinal chemistry and pharmacology of genus Tripterygium (Celastraceae). Phytochemistry. 2007;68(6):732-66.
16- Cui W, Li L, Li D, et al. Total glycosides of Yupingfeng protects against bleomycin-induced pulmonary fibrosis in rats associated with reduced high mobility group box 1 activation and epithelial–mesenchymal transition. Inflammation Research. 2015;64:953-61.
17- Shen Y, Zhao HL, Du J, et al. Feitai, a Chinese herbal medicine, reduces transforming growth factor-β1 and monocyte chemoattractant protein-1 expression in bleomycin-induced lung fibrosis in mice. Clinical and experimental pharmacology and physiology. 2005;32(12):1071-7.
18- An SM, Ding QP, Li L-s. Stem cell signaling as a target for novel drug discovery: recent progress in the WNT and Hedgehog pathways. Acta Pharmacologica Sinica. 2013;34(6):777-83.
19- Yang J, Cui Y, Kolb M. How useful is traditional herbal medicine for pulmonary fibrosis? Respirology. 2009;14(8):1082-91.
20- Zhang XM, Sun XS, Jiang LD, Yang XH, Zhou PA. Treatment of idiopathic pulmonary fibrosis with Qi-hong Decoction. J. Beijing Univ. Tradit. Chin. Med. (Clin. Med.) 2007; 14: 9–11. [Article in Chinese].
21- Qiu ZN, Pan JH, Yu QH. Treatment of idiopathic pulmonary fibrosis with Tao-er-dan decoction. Sci. Tradit. Chin. *Med.* 2002; 9: 174–5. [Article in Chinese].
22- Liu LL, Zhang K, Ou JQ. The effect of Bu-shen-yi-fei-fang combining small dose prednisone on pulmonary fibrosis secondary to rheumatoid arthritis. J. Liaoning Tradit. Chin. *Med.* 2006; 33: 849–50. [Article in Chinese].
23- Li H, Du S, Yang L, et al. Rapid pulmonary fibrosis induced by acute lung injury via a lipopolysaccharide three-hit regimen. Innate immunity. 2009;15(3):143-54.
24- Gauldie J, Kolb M, Ask K, et al. Smad3 signaling involved in pulmonary fibrosis and emphysema. Proceedings of the American Thoracic Society. 2006;3(8):696-702.
25- Wong C, Lam C, Wu A, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clinical & Experimental Immunology. 2004;136(1):95-103.
26- Glass WG, Subbarao K, Murphy B, et al. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. The Journal of Immunology. 2004;173(6):4030-9.
27- Zhou X-M, Huang M-M, He C-C, et al. Inhibitory effects of citrus extracts on the experimental pulmonary fibrosis. Journal of ethnopharmacology. 2009;126(1):143-8.
28- Zhang H-Q, Yau Y-F, Szeto K-Y, et al. Therapeutic effect of Chinese medicine formula DSQRL on experimental pulmonary fibrosis. Journal of ethnopharmacology. 2007;109(3):543-6.
29- Tang D, Kang R, Livesey KM, et al. Endogenous HMGB1 regulates autophagy. Journal of Cell Biology. 2010;190(5):881-92.

30- Oruqaj G, Karnati S, Kotarkonda LK, et al. Transforming Growth Factor-β1 Regulates Peroxisomal Genes/Proteins via Smad Signaling in Idiopathic Pulmonary Fibrosis Fibroblasts and Transgenic Mouse Models. The American Journal of Pathology. 2023;193(3):259-74.
31- Ng L-T, Yen F-L, Liao C-W, et al. Protective effect of Houttuynia cordata extract on bleomycin-induced pulmonary fibrosis in rats. The American journal of Chinese medicine. 2007;35(03):465-75.
32- Du S, Li H, Cui Y, et al. Houttuynia cordata inhibits lipopolysaccharide-induced rapid pulmonary fibrosis by up-regulating IFN-γ and inhibiting the TGF-β1/Smad pathway. International Immunopharmacology. 2012;13(3):331-40.
33- Zhai H, Hhang J, Gao M, et al. Comparative study between Ephedra sinica Stapf and Fructus Schisandrae Chinensis on ET-1 and 6-keto-prostaglandin F1α in rats with idiopathic pulmonary fibrosis. Genetics and Molecular Research. 2014;13(2):3761-71.
34- Chen M, Cheung FW, Chan MH, et al. Protective roles of Cordyceps on lung fibrosis in cellular and rat models. Journal of ethnopharmacology. 2012;143(2):448-54.
35- Zhao P, Zhou W-C, Li D-L, et al. Total glucosides of Danggui Buxue Tang attenuate BLM-induced pulmonary fibrosis via regulating oxidative stress by inhibiting NOX4. Oxidative Medicine and Cellular Longevity. 2015;2015.
36- Gao M, Zhang J-H, Zhou F-X, et al. Angelica sinensis suppresses human lung adenocarcinoma A549 cell metastasis by regulating MMPs/TIMPs and TGF-β1. Oncology reports. 2012;27(2):585-93.
37- Menou A, Duitman J, Crestani B. The impaired proteases and anti-proteases balance in Idiopathic Pulmonary Fibrosis. Matrix Biology. 2018;68:382-403.